The University of Jordan
Authorization Form

I, am alaa Ahmed al-Taher authorize the University of Jordan to supply copies of my Thesis/Dissertation to libraries or establishments or individuals on request.

Signature: آلاء احمد الطاهر
Date:

الجامعة الأردنيـــة
كلية الدراسات العليا

التاريــــخ: / /

نموذج رقم (١٨)
اقرار والتزام بقوانين الجامعة الأردنية وأنظمتها وتعليماتها لطلبة الماجستير

أنا الطالب: آلاء احمد الطاهر . الرقم الجامعي: 8090239 .
التخصص: علوم الصيدلانية . الكلية: الصيدلة .

اعلن بأنني قد التزمت بقوانين الجامعة الأردنية وأنظمتها وتعليماتها وقراراتها السارية المفعول المتعلقة باعداد رسائل الماجستير والدكتوراة عندما قمت شخصيا" باعداد رسالتي / اطروحتي بعنوان: ....
تحضير الحبيبات للمواد الفعالة الذائبة في الماء والمحضرة
باستخدام طريقة تحضير المذيب ودراسة أثر تغيير بعض
عوامل التحضير على شكل الحبيبات وإطلاق المادة الفعالة منها
....

وذلك بما ينسجم مع الأمانة العلمية المتعارف عليها في كتابة الرسائل والأطاريح العلمية. كما أنني أعلن بأن رسالتي /اطروحتي هذه غير منقولة أو مستلة من رسائل أو أطاريح أو كتب أو أبحاث أو أي منشورات علمية تم نشرها أو تخزينها في أي وسيلة اعلامية، وتأسيسا" على ما تقدم فانني أتحمل المسؤولية بأنواعها كافة فيما لو تبين غير ذلك بما فيه حق مجلس العمداء في الجامعة الأردنية بالغاء قرار منحي الدرجة العلمية التي حصلت عليها وسحب شهادة التخرج مني بعد صدورها دون أن يكون لي أي حق في التظلم أو الاعتراض أو الطعن بأي صورة كانت في القرار الصادر عن مجلس العمداء بهذا الصدد.

توقيع الطالب: آلاء احمد الطاهر التاريخ: / /

تعتمد كلية الدراسات العليا
هذه النسخة من الرسالة
التوقيع .... التاريخ ٢٦/١١/٢٠١١

FORMULATION OF MICROPARTICLES WITH WATER SOLUBLE DRUGS BY SOLVENT EVAPORATION TECHNIQUE USING EUDRAGIT NM AND THE STUDY OF THE EFFECT OF DIFFERENT PROCEDURES VARIABLES AND ADDITIVES ON THE PROPERITIES ON THE PROPERTIES OF THE PREPARED MICROPARTICLES AND PRODUCT RELEASE.

By

Alaa Ahmed al- Taher

Supervisor

Dr. Bashar ALKHALDI

This thesis was submitted in partial fulfillment of the requirements for the master degree in pharmaceutical degree in pharmaceutical sciences

Faculty of graduate studies

The University of Jordan

October, 2011

Committee Decision

This thesis/ Dissertation (Formulation of microparticles with water soluble drugs by solvent evaporation technique using Eudragit NM and the study of the effect of different procedure variable and additive on the properties on the properties of the procedure microparticles and product release) was successfully Defended and Approved on October, 2011).

<u>Examination Committee Signature</u>	<u>Signature</u>
Dr. Bashar ALKHALDI, supervisor Associate professor of pharmaceutical technology	....
Dr. Hatim ALKHATIB, member Associate professor of pharmaceutical technology	....
Dr. Mohammed KHALIL LAHAM , member Associate professor of pharmaceutical sciences	....
Dr. Aymman KHDAIR, member Assistant professor of pharmaceutics Applied Science University	....

Dedication

This thesis is dedicated to everyone that helped me to fulfill it including my family, research assistants and professors.

To everyone that has given me support and faith to accomplish it.

To everyone that has been a great source of motivation and engorgement to achieve my work.

To my university that is considered to be the mother of universities in Jordan.

Acknowledgment

From the first stages of this thesis to final drafts, I owe all my gratitude to my supervisor who has given me guidance, support and advice.

All thanks and respect to my doctors and professors in pharmacy faculty who has been a source of knowledge for me to accomplish my work.

My deepest appreciation to my Lab College, friends and research assistants that have been a source of motivation and guidance for me to complete my work.

To everyone that has been generous and supportive.

List of contents

List of Tables

List of figures

List of figures

List of abbreviations

Number	Symbol/Abbreviations	Definition
1	o/w	Oil in water emulsion.
2	B.P	British pharmacopoeia.
3	HLB	Hydrophilic lipophilic balance.
4	SLS	Sodium lauryl sulfate.
5	$D_{0.5}$	Median particle diameter.
6	$D_{0.1}$	Particle size below which 10% of the microparticles lies.
7	$D_{0.9}$	Particle size below which 90% of the microparticales lies.
8	µm	Micrometer.
9	ml	Milliliter.
10	DSC	Differential scanning Calorimetry.
11	F_2	Similarity factor.
12	PL68	Pluronic F68.
13	TW 20	Tween 20.
14	δ	Monodispersity index.
15	Ƶ	Zeta potential.
16	N_D	Drug loading.
17	D_d	Diameter of one drop.
18	(v/v)	Volume per volume.

19	N	Agitation rate (turns/min).
20	d_{max}	Maximum diameter.
21	φ	Viscosity.
22	MFT	Minimum forming temperature.
23	Tg	Glass transitional temperature.
24	CR	Controlled release.
25	TMAEMACL	Trimethylammonioethyl methacrylate chloride.
26	MMA	Methyl methacrylic acid.
27	EA	Ethyl acrylic acid.
28	HPMC	Hydroxyl propyl methyl cellulose.
29	PVA	Poly vinyl alcohol.

FORMULATION OF MICROPARTICLES WITH WATER SOLUBLE DRUGS BY SOLVENT EVAPORATION TECHNIQUE USING EUDRAGIT NM AND THE STUDY OF THE EFFECT OF DIFFERENT PROCEDURES VARIABLES AND ADDITIVES ON THE PROPERITIES ON THE PROPERTIES OF THE PREPARED MICROPARTICLES AND PRODUCT RELEASE.

By
Alaa Ahmed al- Taher

Supervisor
Dr. Bashar ALKHALDI

Abstract

Solvent evaporation technique was used to prepare different Eudragit NM and Eudragit RL theophylline loaded microparticales at different ratio. Two type of formulas were prepared one free from surfactants and the other formulas were emulsified using three different surfactants Sodium lauryl sulfate, Tween 20 and Lutrol F 68.

Theophylline loaded microparticales were prepared using different formulation variables including temperature (25°c and 40 °c), volume fraction of the dispersed phase to the continuous phase (5, 10, and 15%) and quantities of theophylline in the dispersed phase (5, 15 and 25%) of the polymer weight respectively. These microparticales were assessed in terms of their release behaviors, particles size and loading efficacies.

It was noticed that as the fraction of the Eudragit NM increases the encapsulation efficacy increases, also the incorporation of surfactants Tween20 and Lutrol F 68 were capable to increase the encapsulation significantly, when compared to SLS. Temperature was capable to decrease the encapsulation efficacy by 10%, compared to the formula that was prepared at room temperature.

Introduction

1. Multi – particulate system.

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05 - 2.00 mm (Shaji J., al. 2007). To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into tablets (Pharma Polymers, November 2002). Multiparticulates are discrete particles that make up a multiple unit system. They provide many advantages over single-unit systems because of their small size. Multiparticulates are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation (Tang E. S.K. al., 2005).

Recently more emphasis is being laid on the development of multiparticulates dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying (Laila F. A.A. al., 2006).

There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children (PharmaPolymers, November2002). Multiparticulates systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations.

After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract. If these subunits have diameters of less than 2mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability (PharmaPolymers, November2002).

Drug safety may also be increased by using multiparticulates dosage forms, particularly for modified release systems. For example, if the film coat of a single-unit (monolithic) enteric coated tablet is damaged, the complete dose will be released into the stomach where it may cause pain or ulceration or reduced efficacy, depending on the reason for choosing the protection of the enteric coating. Equally, if there is damage to the film coating of a monolithic tablet with a sustained release formulation, this can lead to "dose dumping" and result in dramatic side effects.

By contrast, in multiparticulate formulation, the release characteristics are incorporated into every single subunit and any damage only affects the release behavior of the subunit involved, which represents a small part of the total dose, reducing the likelihood of safety problems (PharmaPolymer, November2002).

1.1 Advantages of oral multiparticulate controlled drug delivery system:

Multiparticulate systems could be formulated as liquid suspensions and thus allowing flexibility in dosing (Adeyey, et al., 2005), oral multiparticulate controlled drug delivery systems offer several advantages compared to single unit dosage forms including:

- Lower intra and inter subject variability in gastric emptying times (Ghebre – Sellassie and Gandhi, et al. as cited in siepmann et al., 2006).

- More homogenous distribution within the content of the gastrointestinal tract resulting in more uniform drug absorption and reduced local irritation (Cuna, et al., 2000, Ray, et al 2005, Siepmann et al., 2006).
- Reduction of dose dumping (Siepmann et al., 2006).
- Higher oral dosing with relativity reduced side effects (Ray, et al., 2005).

1.2 Disadvantages of oral multiparticulate controlled drug delivery systems:

Suspensions containing controlled release dispersed microparticales are more complex than solid dosage forms because of interactions that can occur (Cuna, et al., 2000). These interactions include drug – excipient interaction as studied by (Adeyeye, et al., 2006).

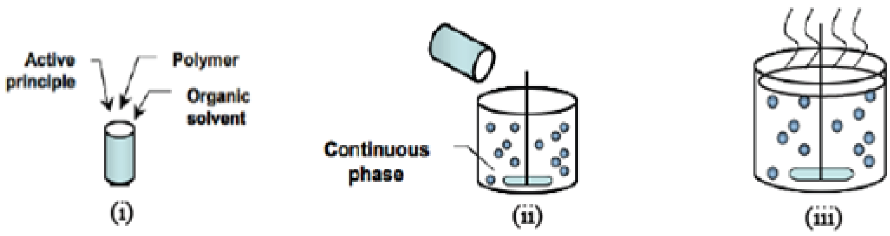
- Reduction of dose dumping (Siepmann et al., 2006).
- Higher oral dosing with relatively reduced side effects (Ray, et al., 2005).

1.3 Technique of microencapsulation and their application:

The technique of microencapsulation by solvent evaporation is applied in pharmaceutical industries to obtain controlled released of a drug. The obtained polymer microspheres with drug trapped inside can degrade and release the encapsulated drug slowly with a specific release profile.

This controlled drug release has outstanding clinical benefits: reducing of dosing frequency, more convenience and acceptance for patients, and drug targeting to specific locations resulting in a higher efficiency (Berkland et. al., 2002; Freiberg and Zhu, 2004).

1.4 Methods for microencapsulation by solvent evaporation technique:



Basic steps of microencapsulation by solvent evaporation

There are many methods for microencapsulation by solvent evaporation technique. The choice of the method that will give raise to an efficient drug encapsulation depends on hydrophillicity or the hydrophobicity of drug.

1.4.1 Oil – in- Water (O/W) methods.

This method is used for water insoluble drugs or poorly water soluble drugs, which is considered to be the simplest, with the following steps (Herrmann and Bodmeier, 1998):

- Dissolution of the hydrophobic drug in an organic solvent containing the polymer.
- Emulsification of the organic phase called the dispersed phase in the continuous phase.
- Extraction of the solvent from the dispersed phase in the aqueous phase called the continuous phase accompanied by solvent evaporation transforming the droplets of the dispersed phase into solid particles.
- Recovery and drying of the microspheres to eliminate the residual solvent.

The methods for (O/W) include:

1. The (o/w) co-solvent method: when the drug is not soluble in the main organic solvent, a second solvent called co-solvent is necessary to dissolve the drug.
2. The (o/w) dispersion method: the drug is dispersed in form of solid powder in the solution of polymer and organic solvent.

Examples of hydrophobic drugs encapsulated using solvent evaporation techniques cyclazocine (narcotic antagonists), (Li et al. 1999a), Lidocaine (local anesthetics), (Chung et al., 2001), Progesterone (hydrophobic steroids), (Aso et al.l, 1994).

1.4.2 The (W/O/W) double emulsion method.

The aqueous solution of hydrophilic drug is emulsified with organic phase (w/o); this emulsion is then dispersed into a second aqueous solution forming a second emulsion. (w/o/w), e.gv insulin Meinel et al. (2001), Singh et al. (2001), proteins Li et al. (2000b), vaccines Little et al. (2005), Azevedo et (2006), Feng et al. (2006).

1.4.3 The Oil – in – Oil (O/O) method:

In this technique the continuous phase is replaced by oily phase. e.g., encapsulation of insulin Mana et al (2007),Furtado et al. (2006), proteins Dai et al.(2005), peptides Luan et al. (2006).

2. The choice of the materials.

2.1 The dispersed phase (polymer).

The biodegradability or biocompatibility is an essential property for the polymer that is used for pharmaceutical application. Biodegradability means the separation of the polymer into harmless component, and shouldn't cause any physiological effect.

Polymers and copolymers of lactic and glycolic acids are the most commonly used to develop drug delivery systems due to their safe and FDA (Food and Drug Administration) approved applications in humans (Chulia et al., 1994).

Non-biodegradable polymers with good biocompatibility are used as drug carriers such as ethyl cellulose, and polymethyl methacrylate (biocompatible but non-degradable). Ethyl cellulose can be administered orally to protect drug from gastrointestinal tract (Fatome et al., 1987), or administered intradoudenally for prolonged release in intestine (Takishima et al., 2002).

Polymethyl methacrylate microspheres are used extensively as polymers for releasing antibiotic for bone infections (such as osteomyelitis), (Stallman et al., 2006) and surgical removal is required after wards because the polymethacrylate require surgical removal is required after wards.

Polymethyl methacrylate is not degradable and it is used as a model polymer for big scale optimization. The choice of the polymer used as drug carrier depends on the drug nature and on the release rate, which is determined by the polymer physical properties, if a single polymer can't achieve the required release rate a co-polymer could be used, co-polymer (PEG/PLA) was synthesized from (PEG) and a polylactic acid in order to increase the degradation rate, the presence of (PEG) enhance the diffusion of water through the polymer (Zhu et al., 1990).

2.2The solvent used:

A suitable technique for microencapsulation by solvent evaporation should meet the following criteria:

1. Being able to dissolve the chosen polymer.
2. Being poorly soluble in the continuous phase.
3. Having a high volatility and a low boiling point.

4. Having low toxicity.

The main solvent used in literature is chloroform was frequently used before but due to its toxicity, which is gradually replaced by Methylene chloride (Maia et al. 2007).

Methylene chloride is the most common solvent for encapsulation for solvent evaporation technique because of its high volatility, low boiling point and high miscibility with water.

However, this solvent is confirmed to be carcinogenic according to EPA (Environmental Protection Agency), Yang et al. (2000a), Yang et al. (2000b), Berchane et al. (2006).

Ethyl acetate shows promising potential as less toxic substitute of methylene chloride due to its partial miscibility in water and accordingly, there are three methods that are available:

1. Aqueous solution that is saturated with the organic solvent (Bahl and Sah, 2000).
2. The dispersed phase is dispersed first then emulsified in a little aqueous solution, after the formation of drops this emulsion is emulsified with large quantity of aqueous solution, after the formation of drops this emulsion is poured into large quantity of aqueous solution (Freytag et al., 2000).
3. The dispersed phase is emulsified in a little quantity of aqueous solution, and then agitated until complete evaporation of the organic solvent is achieved leading to solidification of microspheres (Sah, 1997).

2.3 Surfactants:

*Surfact*ants are responsible for dispersing one phase into the other. They act by stabilizing the dispersed phase into the continuous which will consequently prevents the coalesance and phase separation. Before choosing the surfactant type and concentration, it is important to know the relative polarity of the two phases.

Surfactants are amphiphillic in their nature; they contain two parts polar head that is oriented toward the water and the hydrocarbon chain (hydrophobic) part that is oriented toward the organic phase.

There are four types of surfactants: anionic, cationic, amphoteric and non- ionic. The anionic surfactants release the negative charge toward the aqueous solution, while the amphoteric surfactants behave as anionic in alkali PH and as cationic in acidic media, e.g. of anionic surfactants: sodium dodecylsulphate (SDS). They have a relatively high HLB (hydrophilic –lipophilic balance). The cationic surfactants on the contrary release a positive charge in aqueous solution. Non-ionic surfactants have no charge, e.g partially hydrolyzed PVA (polyvinyl alcohol) (André- Abrant et al., 2001), methylcellulose (Berchane et al., 2006), tween (Yang et al., 2000a) and span (Jalil and Nixon, 1990).

According to the study done by (Yang et al., 2001), it was concluded that as the concentration of the surfactant increases the size of the dispersed phase decreases.

3. Effect of the operating conditions:

The impact of the operating conditions on the properties of the formed microspheres as the inner structure is evaluated in the following headlines.

3.1 Viscosity of the internal phase.

The effect of the internal viscosity on the size of the microspheres is described according the following equation (Calderbank, 1958):

$$d_{32}= A\ (\mu_d/\mu_c)^{0.25}$$

Where d_{32} is the average diameter (Sauter's diameter) of the microspheres, μ_d is the viscosity of the internal phase, μ_c the viscosity of the continuous phase and A is the coefficient.

The Addition of additives might lead to increase in continuous phase viscosity, also increasing both concentration and the molecular weight of the polymer lead to increase in the encapsulation efficiency both are proved by the work of (André-Abrant et al., 2001) , in which the ethyl benzoate (drug model) is encapsulated more efficiently in ethyl cellulose by increasing both.

It appears that increasing the viscosity of the internal phase leads to increase in the size of the formed microspheres and leads to increase in the encapsulation efficiency.

3.2 The quantity of the drug in the dispersed phase:

It was observed that increasing the quantity of drug concentration may lead to increase in the encapsulation efficacy (André-Abrant et al., 2001). However, when too much of drug is loaded into the microparticales it will lead to creation of porous microparticales having more irregular shapes (Witschi and Doelker, 1998). The more porous the microparticales, the higher is the drug loss.

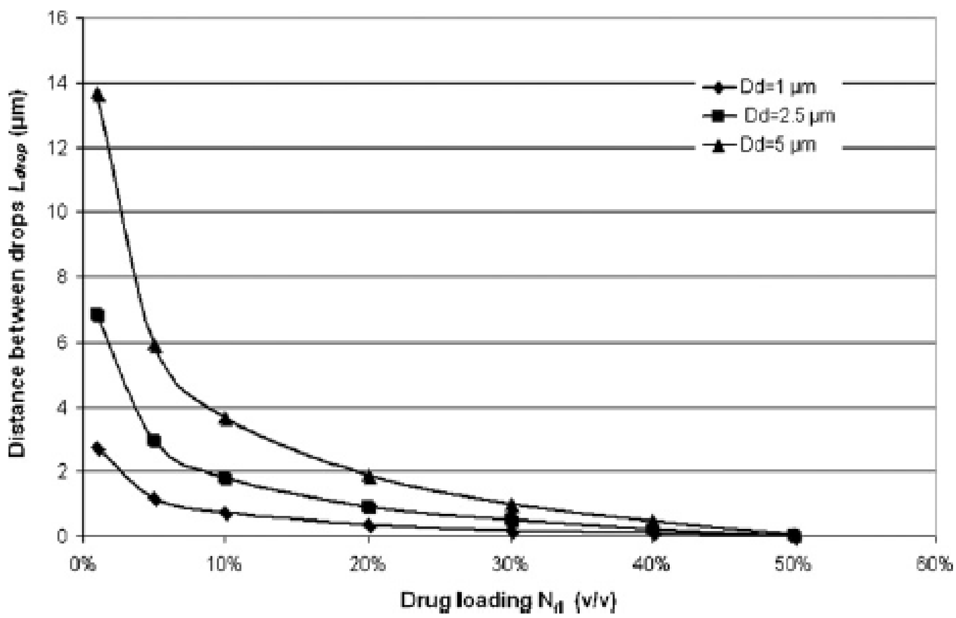
This could be explained by assuming that the drug is homogenously dispersed inside the microsphere and the drug forms spherical drops and the distance between them is equal considering, that the drug loading is N_d (v/v) % and the diameter of one drop (D_d) in the cubic space inside the microsphere of length L, N_d can take the following form: (Maa and Hsu, 1996).

$$N_{\mathrm{d}} = \frac{(\pi/6)D_{\mathrm{d}}^{3}}{L^{3}} \quad (1)$$

The distance between two drops in the dispersed phase can be expressed as function of N_d and D_d from equation (1):

$$L_{drop} = D_d \left[\left(\frac{\pi}{6N_d} \right)^{1/3} - 1 \right] \quad (2)$$

The relation between the distance of droplets and the drug loading is expressed as the following:



It's better to increase the size of the droplet to have big distance between droplets to avoid the coalescence.

However, the size of the dispersed phase droplets should remain reasonable as the droplet size increases, this will lead to a decrease in droplet stability, and accordingly the drug loading will decrease. (Maa and Hsu, 1996).

Moreover, during the solidification of microsphere, the microsphere shrinks because the volume of drug remains the same; the volume percentage of the drug becomes much more important than its initial value N_d.

In order to assure an efficient drug encapsulation, the drug loading should respect the limit order to assure an efficient drug encapsulation (Maa and Hsu, 1996).

3.3 Agitation, geometries and size prediction:

Agitation is one of the most important parameter for controlling the size of the microspheres, after the physico - chemical properties of the polymer material. There are many factors that are related to the agitation and affect the particle size the geometry of the reactor, the number of impellers and its position (Maa and Hsu, 1996).

There are many correlations that predict the size and size distribution of the droplets in the emulsion of the two immiscible liquids (Haas, 1987; Kumar et al., 1993; Maa and Hsu, 1996).

The correlations take into account two aspects:

(1) The physical properties of materials, such as the density of continuous phase and the interfacial tension.

(2) The factors linked to agitation.

The most basic and employed correlation is based on the theory of Kolmogoroff (Hinze, 1955), it is expressed as:

$$\frac{d_{max}}{D} = c_1 \left(\frac{\rho_c N^2 D^3}{\sigma} \right)^{-3/5} \tag{3}$$

d_{max} is the biggest drop size which can exist under turbulence; d is the diameter of the agitation pc is the density of the continuous phase(kg/m_3).

N is the agitation rate (turns/s); δ is the interfacial tension between the two immiscible liquids, (Haas, 1987; Kumar et al., 1993).

Its takes into account two aspects:

1. The physical properties of the material such as the density of the continues phase and the interfacial tension.
2. The factors linked to agitation.

The most basic and the most employed correlation is based on the theory of Kolmogoroff (Hinze, 1955), it is expressed as the following:

$$\frac{d_{max}}{D} = c_1 \left(\frac{\rho_c N^2 D^3}{\sigma} \right)^{-3/5} \quad (4)$$

d_{max} is the biggest droplet size which can exist under turbulence, D is the diameter of the agitator (m),ρc is the density of the continuous phase (kg/m3).

N is the agitation rate (turns/s), δ is the interfacial tension between the two immiscible liquids (N/m) and c_1 is constant.

The average size such as sauter's diameters d_{32} can be estimated; since it is proportional to the maximum diameter d_{32} can be estimated of drop d_{max} (Hinze, 1955).

d32 = c2dmax (5)

C_2 is constant. It is clear that from equation (3) and (4) that increasing the agitation rate will lead to decrease in the average size of the dispersed phases confirmed in the literature (Gabor et al., 1999; André-Abrant et al., 2001; Yang et al., 2001; Mateovic et al., 2002).

Other terms were introduced into equation (4) in order to include other factors such as the volume fraction of the dispersed phase to the continuous phase φ and viscosity ratio (Calder bank et al, 1958).

$$\frac{d_{32}}{D} = c_3(1 + c_4\Phi)\left(\frac{\rho_c N^2 D^3}{\sigma}\right)^{-3/5}$$

(6)

$$\frac{d_{32}}{D} = c_5\Phi\left(\frac{\rho_c N^2 D^3}{\sigma}\right)^{-3/5}\left(\frac{\mu_d}{\mu_c}\right)^{0.25}$$

(7)

In the previous equations the constants $c_{3,}$ c_4 and c_5 are constants. The value of c_5 φ ((ρc $N^2D^{3)}$ δ)$^{-3/5,}$ D is equal to that of coefficient (A) mentioned in equation (1). Increasing the diameter of the dispersed phase leads to decrease in the size of the microspheres as proven in the following literatures, (André-Abrant et al., 2001) on other hand other studies showed no significant change (Gabor et al., 1999).

3.4 Temperature effect:

3.4.1 Disadvantage of elevating of temperature:

As the temperature increases, this will lead to increase in the evaporation rate of the continuous phase **(**Miyazaki et al., 2006), or the evaporation rate could be increased by reducing the pressure in reactor **(**Meng et al., 2004).

However, there are draw backs on elevating the temperature that the recovered total mass is reduced and the size distribution shift toward larger size and drug encapsulation efficiency decreases, also the particles become coarser (Freitaset al., 2004), taking into consideration that elevating the temperature may lead to denaturation of the drug. Elevation of the temperature leads to coarser and larger particle with lower loading efficacies.

4. Poly (meth) acrylate Applications:

More than 70 years ago, poly (methyl methacrylate) (PMMA), was invented as a crystal-clear, unbreakable organic glass of outstanding quality.

With the trademark Plexiglas®, it achieved worldwide recognition as a unique synthetic material and a symbol of technical progress.

The excellent biocompatibility of PMMA was detected early and it was used for artificial limbs and implants. PMMA is also well tolerated by the skin and the mucosa, so that dental prostheses and contact lenses made of PMMA are used even today.

Many medical tools that come into direct contact with blood are made from PMMA or similar copolymers. Macroporous oxidant acrylic beads, commercialized under the trade name Eupergit®, gained significant importance in chemical and medical applications. Enzymes covalently immobilized on Eupergit serve as highly stable, recyclable catalysts in industrial biotransformation (Katchalski-Katzir 2000).

The polymer does not activate the coagulation of blood; it is also used as an adsorbent for blood purification in extracorporeal therapy (Bosch T, Wendler T, 2004). Specialty stationary phases for chromatographic separation of bimolecular were developed from Eupergit (Solomon B al., 1992).

5. Definitions of Latexes and Their Physicochemical Specifications:

The term *latex* is often used for aqueous polymer dispersions. It originally described rubber latex, which is called *natural latex*, in contrast to *synthetic latexes*, which are preferably prepared by emulsion polymerization (Banker GS al., 1981).

A polymer dispersion or latex is characterized by a particle size between 10 and 1000 nm. In the technical field of polymer applications, the terms dispersion*s* and *latexes* are used synonymously. Systems of smaller particle sizes are called *microemulsions* or *colloidal solutions*.

They are nearly transparent and exhibit the Tyndall effect in a light beam. The term *minimum film-forming temperature* (MFT) is the temperature in degrees Celsius above

which a continuous film is formed from dispersions under distinct drying conditions (ISO/DR 2115. Deutsches Institut fŸr Normung E.V. 53, 787).

Film formation is correlated to the glass transition temperature (*T*g) of the polymer itself, which is defined as that temperature at which the viscosity of a melted thermoplastic polymer increases considerably, while the temperature is continuously decreasing. In molecular terms, this is the temperature at which the flexibility of polymer chains and thus their material properties change. One widely used method for the determination of *T*g is the differential scanning calorimetric method described by Turi (Turin EA, ed., 1981).

5.1 Types of Latex polymers used in microparticles preparation:

5.1.1 Neutral Polymers

Latexes are formed by emulsion polymerization of MMA and EA. The polymer is commercialized as Eudragit NE 30 D/NE 40 D and Eudragit NM 30 D.

The latter provides a broader application range due to the use of polyethylene glycol-600 stearyl ether NF as an emulsifier. Drug release is controlled by coating thickness.

IN addition to the coating of small particles, such as crystals, granules, and pellets the polymer gained significant importance in the formulation of controlled-release tablets. Particularly, Eudragit NM 30 D can be used in wet granulation processes as a binder for controlled release (CR) matrix tablets (EUDRAGIT® specifications, Evonik industries). Initiators, preferably peroxides, start the polymerization process by forming radicals and are included as end groups in the polymer chains. Chain transfer agents, which moderate the molecular weight, react with polymer radicals and are also found as terminal groups in the polymer chains. To obtain free-flowing granules, bulk polymers are extruded. During the extrusion process, volatile components of the polymer raw material such as residual monomers, solvents, and polymerization modifiers can be

evaporated by vacuum. However, the limited thermal stability of functional groups in methacrylate copolymers has to be considered (Petereit HU al., 1999).

5.1.2 Ionic polymer

In order to expand the variability in the release kinetics from controlled-release single and multiunit dosage forms, hydrophilic polymers containing trimethylammonio ethyl methacrylate chloride (TMAEMACl) as hydrophilic moieties have been developed. Eudragit RL, carrying 10% (w/w) TMAEMACl, provides relatively high permeability, while Eudragit RS includes 5% (w/w) only (Lehmann K.al., 1986).

The polymers are synthesized by bulk polymerization and can be mixed in any ratio for optimized drug-release profiles. The polymers swell in water depending on their content of hydrophilic quaternary ammonium group (Lehmann K.al., 1986).

Since quaternary ammonium groups dissociate completely in physiological media of pH 1 to 8, the permeability of coatings was found to be pH independent.

Their particular value in controlled-release dosage forms is based on their miscibility in any ratio Thus; release kinetics can be adjusted to accommodate pharmacokinetic needs and the solubility of the active compound (Lehmann K.al., 1986).

6. Theophylline as a candidate drug for this study:

Theophylline (figure 2) was chosen as a candidate for this study for several reasons one of which is wildly available, not costly and it's slightly soluble in water.

In addition to that, theophylline is easily analyzable spectrophotopmetrically at 272 nm. Despite theophylline being widely available in a large number of proprietary preparations, little is known about its mode of action.

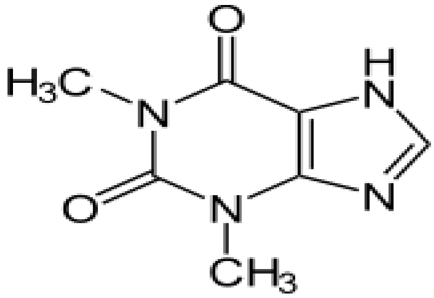


Figure 2: Molecular structure of theophylline (B.P, 2005).

7. Objective and Hypothesis of the current study:

7.1 Objectives:

The objectives of this research where:

- To determine the optimum drug/polymer, polymer/polymer ratio that produces a sustained release microparticles.
- To study the effect of surfactant level on the release behavior of the drug from microparticles using SLS, Tween 20 and Lutrol F 68.
- To Study the effect of increasing the proportion of the organic phase and the evaporation rate on the shapes and interaction between the polymer and the drug.

7.2 Hypothesis:

Preparation of solid microparticales loaded with theophylline by solvent evaporation technique using EUDRAGIT® NM 30 D that present as an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate with low glass transitional temperature (Tg), which makes it rubbery at room temperature this makes preparation of the microparticales hard and challenging.

The microparticales will be prepared using different types and levels of surfactants Sodium luryl sulphate (SLS), Tween 20 and pluronic 68 at different evaporation rates with different drug / polymer ratios and polymer/polymer ratios and assessing them in terms of their release behavior, size and shapes.

Experimental Part

1. Material and suppliers:

- Anhydrous Theophylline was kindly donated by Sigma Company. It is a white crystalline odorless powder with a bitter taste, which forms salts with acids and water soluble derivatives with alkali metals and amines.

The solubility of theophylline is 1 in 120 of water at 25° c increased from 8 mg per ml in water to 8.3 mg per ml in 30 % w/w sucrose solution. A further increase in sucrose concentration to that of syrup decreases the solubility to 6.2 mg per ml; it is also soluble in ether and chloroform (B.P, 2005).

-Poloxamer 407 (Lutrol® F68, Pluronic F68), which was purchased from BASF, this copolymer is built from ethylene oxide and propylene oxide with HLB value equal 29 (Janinnin, et al., 2006). And it is used as dispersing agent, emulsifier, solubilizing agent and wetting agent (Rowe, et al., 2006).

- Polysorbates 20 (Tween 20) it is a polyoxyethylene 20 sorbitan monolaurate ,which is characterized to be yellow oily liquid at 25 °C, used as emulsifying agent and suspending agent. Its HLB value equal to 16.7 (Rowe, et al., 2006).

- Sodium lauryl sulfate (SLS) (kindly donated by JOSWE, Jordan). It is a white crystalline in its nature colored, odorless granular powder. It has a faint odor of fatty substance that is freely soluble in water and it is particularly insoluble in chloroform and ether, used as anionic surfactant, detergent, emulsifying agent and wetting agent (Rowe, et al., 2006).

- Eudragit NM 30 D provided as a 30% white milky colloidal dispersion, which is a neutral polymer purchased from (Evonik® industries) (Germany). It is composed of MMA (Methyl Methacrylic Acid) and EA monomers (Ethyl Acrylic Acid). It is used as a coating material for small particles, such as crystals, granules, and pellets (Evonik®company specifications, Germany), also the polymer gained significant importance in the formulation of controlled-release tablets due to its plasticizing effect, when it is added to the formulation up to 50%, the coating maintains its enteric behavior and shows significant increase in film flexibility (Lehmann K,. al 1988).It can be used in wet granulation processes as a binder for controlled release (CR) matrix tablets.

-Eudragit RL provided as 30% white colloidal dispersion purchased from Evonik® industries (Germany). It is an ionic polymer hydrophilic, consists of trimethylammonio ethyl methacrylate chloride (TMAEMACl). Monomers, that account for 10% of the polymer monomers, which account for the polymer permeability (Evonik® company specifications).

The polymer is produced by bulk polymerization process and can be mixed in any ratio for optimized drug release. The polymer swells in water depending on the content of hydrophilic quaternary ammonium groups. Since quaternary ammonium groups dissociate completely in physiological media of pH 1 to 8, the permeability of the coatings was found to be pH independent. Its particular value is in controlled-release dosage based on the ratio used (Lehmann K., al 1986). Thus, release kinetics can be adjusted to accommodate pharmacokinetic needs and the solubility of the active compound.

2. Equipment's:

1. Unicam UV2- 100 UV/V is spectrometer, Unicam, England.
2. METTLER TOLEDO DSC 823, Differential Scanning Calorimeter, Mettler, STARe software, Switzerland.
3. Nylon filters with pore size of 0.45μ, PETRATECH, Jordan.
4. Dialysis membrane to perform the process dissolution for the microparticles.
5. Ultra Turrax mixer to perform the process of mixing.
6. Water path to perform a process of evaporation of the organic phase.
7. SHIMADZU, Electronic balance, Shimadzu, Japan.
8. ERWEKA, Dissolution tester, Germany.
9. Digital temperature controller, Poly Science, USA.
10. Telestar Cryodos, Freeze dryer, Spain.

3. Method:

3.1 Preparation of Eudragit (RL, NM) loaded microparticales:

The microparticales was prepared by solvent evaporation technique according the following procedure:

1. Accurate weights of theophylline and Eudragit (NM, RL) were prepared.
2. The polymer was dissolved in a predetermined volume of organic solvent (acetone) using ultra turrax mixer, mixing was continued till a clear solution was formed.
3. Accurate weights of theophylline were added to the above dispersion until it was dispersed completely.
4. The organic phase was evaporated at 40° or 25° C according to the formula prepared.
5. In case of the addition of surfactant, it was dissolved in the aqueous phase, and then the aqueous phase was added gradually to the organic phase as described above. The end point was known when a milky emulsion was obtained.
6. The prepared milky dispersion was left under the mixer until the whole organic phase evaporated then the sample was frozen in a deep freezer at -70° c and then lyophilized in a freeze dryer (- 70 to – 80 °c, 0.1 - 0.2 mBAR) for five days to ensure complete dryness of the microparticles. The samples were collected and sieved using a 750 µm sieve and kept in glass bottles for further studies.

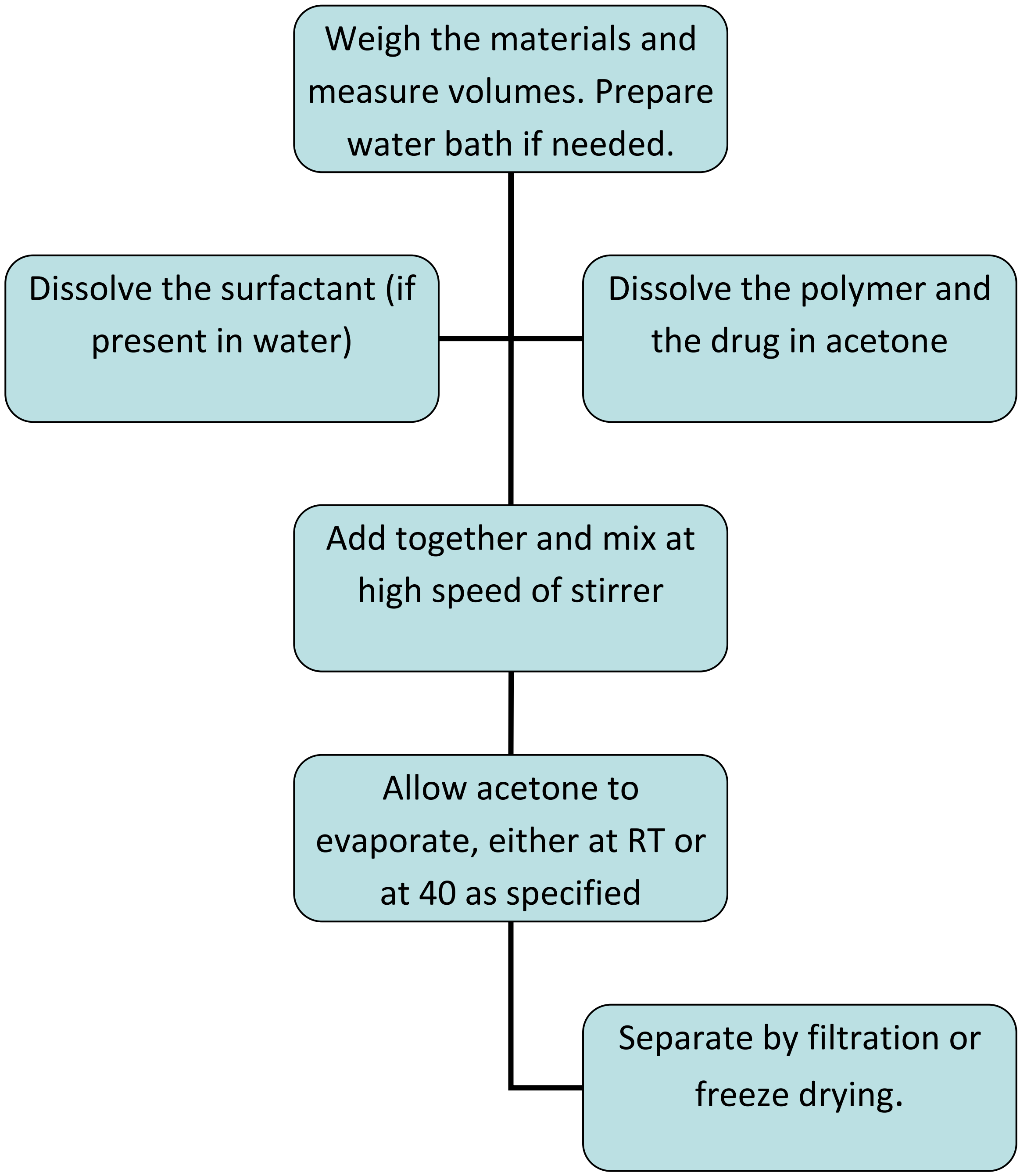


Figure 1: Schematic representation of theophylline – loaded Eudragit NM, RL microparticales by solvent evaporation technique.

3.2 Characterization of theophylline – loaded microparticles:

3.2.1 Particle size measurement:

The size of the particles was analyzed using the lazer diffraction using a Malvern Mastersizer 2000 particle size analyzer.

The measurement was carried as triplicate, the geometrical diameter was expressed in term of volume median diameter ($D_{0.5}$), and monodispersity index (δ) was used to indicate the size distribution and calculated according to the following formula:

$\delta = (D_{0.9} - D_{0.1}) / D_{0.5.}$

Were D0.1 and D0.9 are the particle sizes below which 10% and 90% of the microparticles lies respectively. The smaller the δ value is the better the monodispersity is (Zhang et al. 2008).

3.2.2 Thermal analysis:

Differential scanning calorimetry (DSC) curves were acquired using METTLER TOLEDO DSC 823 with an empty pan as reference. Samples of 5 mg of from selected formulas (using size fraction ≤ 50µm), were placed in aluminum pans Scanning was done at 10°c min^{-1} under 80 ml min^{-1} nitrogen flux at temperature range of 25 – 350 °C.

3.2.3 Determination of drug content:

A sample of 20mg of the microparticles was dispersed in water using 100ml volumetric flask as triplicate and left on the sonicater for 30 min to ensure the complete release the theophylline.

The quantification was carried out by using a validated UV spectrophotometric method using Unicam UV – 100 UV/V spectrometer at 272 nm; samples were filtered using the 0.45 µm nylon filters.

The percentages of drug loading and particle content were estimated as the following: (Actual drug content /Theoretical drug content)* 100.

3.2.4 In – vitro drug release (dissolution):

The Dissolution of theophylline microparticales was tested employing the principle of the dialysis method, using water as the dissolution medium. For this purpose a small samples from each formula were taken and their release behaviors were assessed in triplicate. A 400mg sample weight was placed in each basket and surrounded by dialysis membrane sealed from the bottom, and filled with 5 ml from the dissolution media then it was attached to the USP1 dissolution apparatus (ERWEKA, Dissolution tester), that was sealed from the above.

The dissolution process was carried out in 900ml of water at 37° C with 50 r.p.m.

Aliquots of 5ml samples were withdrawn at predetermined time intervals (0.25, 0.5, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5, 6 and 7 hours). An equal volume of the fresh media, equilibrated at the same temperature, was added after each sampling to maintain sink conditions.

Withdrawn samples were filtered through 0.45µm nylon filters and analyzed spectrophotopmetrically by UV2 – 100 UV/V spectrometer at 272 nm and the results were represented as cumulative percentages of the dissolved drug. All of the values are average results of three independent experiments.

3.3 Experimental design:

3.3.1 Effect of the surfactant type and content on the release behavior of the theophylline –loaded microparticles.

Microparticales containing theophylline and Eudragit NM, Eudragit RL as microencapsulating polymer that were dispersed in the aqueous media using SLS, Tween 20 and Lutrol F 68.

The formed microparticles at different levels of the surfactants ranges from (0.23 – 0.46) g were assessed in term of their in vitro release behavior, drug content and particle size.

Table 1: Formulas prepared to investigate the effect of the surfactant type.

Formula code	Quantities (g)					
	Theophylline	Eudragit NM	Eudragit RS	SLS	Tween 20	Lutrol F 68
SLS – A1	0.12	2	3	0.12	-	-
SLS – A2	0.23	2	3	0.23	-	-
SLS – A3	0.35	2	3	0.35	-	-
SLS – A4	0.46	2	3	0.46	-	-
TW 20 – A1	0.23	1	4	-	0.23	-
TW 20 – A2	0.46	1	4	-	0.46	-
LT – F68 – A1	0.23	1	4	-	-	0.23
LT – F68 – A2	0.46	1	4	-	-	0.46

3.3.2 The effect of the changing the volume fraction of the dispersed phase to the continuous phase.

Microparticales containing theophylline were prepared in different volumes fractions of the dispersed phase containing the drug and the polymer to the aqueous phase.

These formed microparticles then were assessed in terms of their release behavior, drug content and particle size. The relative proportions of the internal phase to external phase are kept constant in order to maintain optimum stability of emulsion.

Table (2): Effect of changing the volume fraction of the dispersed phase to the continuous phase

	Number	Acetone	Concentration Of the polymeric solution	Water	% of the acetone	% of water
Formulas prepared at 100% level EU RS	**Eud(NM,RS) – A1**	119.9	5%	239.8	**33.3 %**	**66.7 %**
	Eud(NM,RS) – V1	56.8	10%	113.6		
	Eud(NM,RS) – V2	42.4	15%	84.98		
Formulas prepared at 80% level EU RS	**Eud(NM,RS) – A2**	119.9	5%	239.8		
	Theo – A1	56.8	10%	113.6		
	Eud(NM,RS) – B2	42.4	15%	84.98		
Formulas prepared at 60% level EU RS	**Eud(NM,RS) – A3**	119.9	5%	239.8		
	Eud(NM,RS) – B1	56.8	10%	113.6		
	Eud(NM,RS) – B3	42.4	15%	84.98		

3.3.3 The effect of changing the theophylline content on the behavior of the theophylline –loaded microparticles.

Microparticales are prepared with different % of theophylline content in order to evaluate its effects on the microparticles that are formed in terms of their release behavior, their size and their encapsulation efficacies.

Table 3: Formulas prepared to investigate the effect of the drug content.

Formula code	Acetone Volume(ml)	Water Volume(ml)	Theophylline content(g)	Theophylline (%)
Theo – A1	56.8	113.6	0.25	5%
Theo – A2			0.75	15%
Theo – A3			1.25	25%

3.3.4 Effect of changing the polymer proportion on the behavior of the theophylline – loaded microparticles.

Microparticales were prepared using mixture of the two Eudragits (Eudragit Nm and RS). In these experiments, Eudragit RS has been used at three different levels: 100%, 80% and 60% .Particles obtained were analyzed in relation to their release behavior, particle size, drug content and the encapsulation efficiency.

Table (4): Formulas prepared to investigate the effect of changing the polymer proportion on drug content.

Formula code	Acetone (ml)	Water (ml)	Eudragit RS (%)	Eudragit NM (%)	Theophylline (g)
Eud(NM,RS)–A1			100%	-	0.75
Eud(NM,RS)–A2	119.9	239.8	80%	20%	0.75
Eud(NM,RS)–A3			60%	40%	0.75

3.3.5 Effect of changing temperature in the theophylline –loaded microparticales.

The microparticales were prepared under elevated temperature (40°C) in a water bath to evaporate the organic phase (acetone). The formed microparticales were evaluated according to its size, drug content, encapsulation efficacy and their release behavior.

Table (5): Formulas prepared to investigate the effect of temperature (40°C).

Formula code	Acetone (ml)	Water (ml)	Eudragit RS (g,%)	Eudragit NM (g,%)	Theophylline (g)
Eud(NM,RS) –T1			100%	-	0.75g
Eud(NM,RS) –T2	56.8	113.6	80%	20%	0.75g
Eud(NM,RS) –T3			60%	40%	0.75g

3.3.5 Statistical analysis:

The release profile of Theophylline – loaded microparticles were evaluated by the calculation of the similarity factor (F_2) according to the following formula: F = 50 Log $((1+(1/n)\square\ ^{n}{}_{t=1}\ (R_{r} - T_{t})^{-0.5})*100)$, where n the number of sample points, R_r And T_t are the reference and the test assays, respectively, at time t. F_2 value more than 50, suggest that the two compared dissolution profiles are similar.

RESULTS AND DISCUSSION

1. Characterization of theophylline – loaded microparticles:

1.1 particle size measurement:

1.1.1 Effect of the surfactant type and concentration on the size of the particle formed.

The effect of different surfactants was evaluated such as SLS, Tween 20 and Lutrol F68. The Addition of SLS as shown in figure (2) lead to an increase in particle size. This effect can be explained by the reduction of zeta potential around the particle due to the presence of counter ions. Accordingly, zeta potential goes below certain value and the attractive forces exceed the repulsive forces, and the particles become together. This phenomenon is known as flocculation. Therefore, the particles become larger in size.

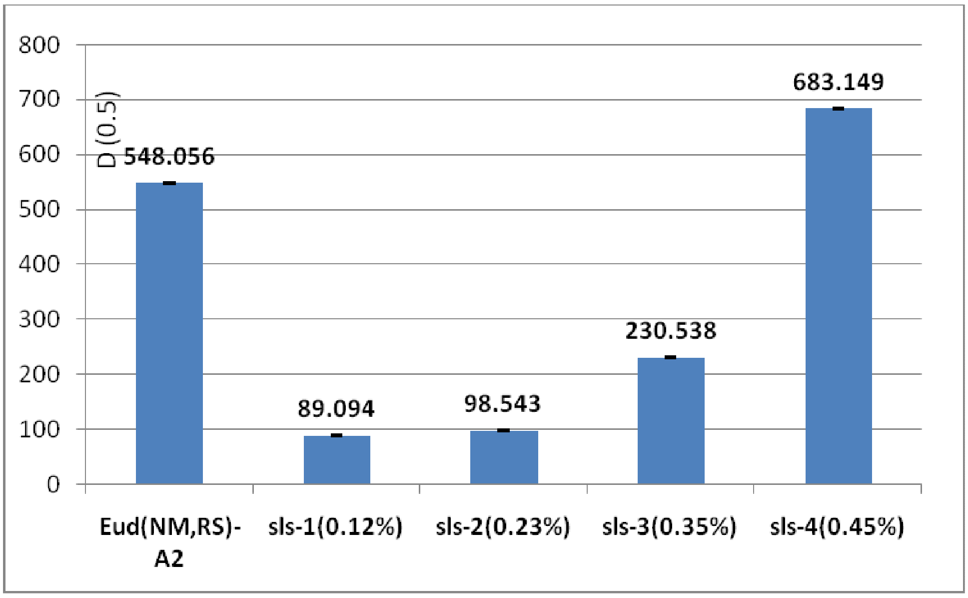


Figure (2): Effect of addition of SLS as stabilizer to the size of the particle formed.

The addition of poloxamer (Lutrol F 68) or leads to decrease in the particle size, this could be explained by the ability of the surfactant to form thick and dense layer around the particle formed the hydrophobic part of the chain formed serves as anchor chain, which adsorb firmly on the particle surface, while stabilizing hydrophilic chain dangle in the dispersion medium to form stabilizer layer. When two particles approach each other, the stabilizer layer may undergo over lap or become compressed. The chains will lose configurational entropy in the overlap region, hence leading to strong repulsion. Polymeric surfactant with longer polymer chain and higher molecular weight is beneficial for the particle stabilization. The same applies for polysorbates where the fatty acid chain is the hydrophobic part and polyoxy ethylene is the hydrophilic one, which can be used to explain the results that showed a decrease in particle size, (Zhang, et al. 2008). The addition of these stabilizers lead to a decrease in the particle size and Lutrol F68 leads to decrease in the particle size more than Tween 20 as shown in figure (3).

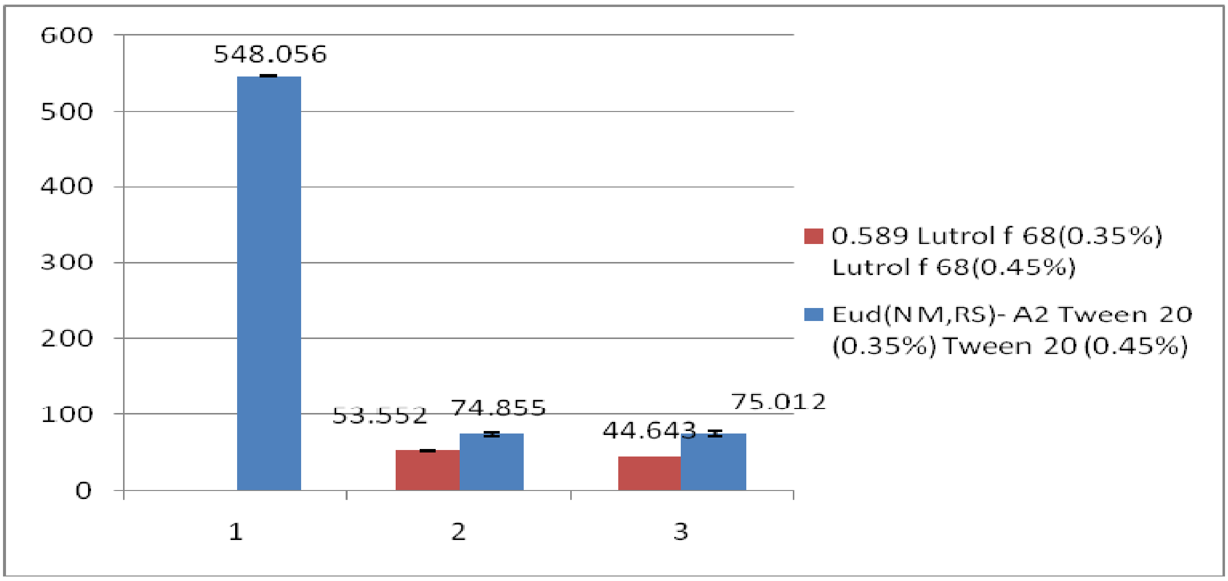


Figure (3): Effect of addition of Tween 20 and Lutrol F 68 as stabilizer on the particle size.

1.1.2 Effect of drug concentration of the dispersed on the particle size.

It appears from the following result that as the percentage of the dispersed phase to the continuous phase increases, there is a slight decrease in the particle size. Once the volume fraction changes from 5% (w/v) to 10 % (w/v), and when the concentration of the internal phase approaches 15% (w/v), the size of the dispersed microspheres increases, accordingly the size of the particles become larger. This was explained by the work of Yang et al. (2000a), a higher polymer (ethyl cellulose) concentration results in a higher particle size.

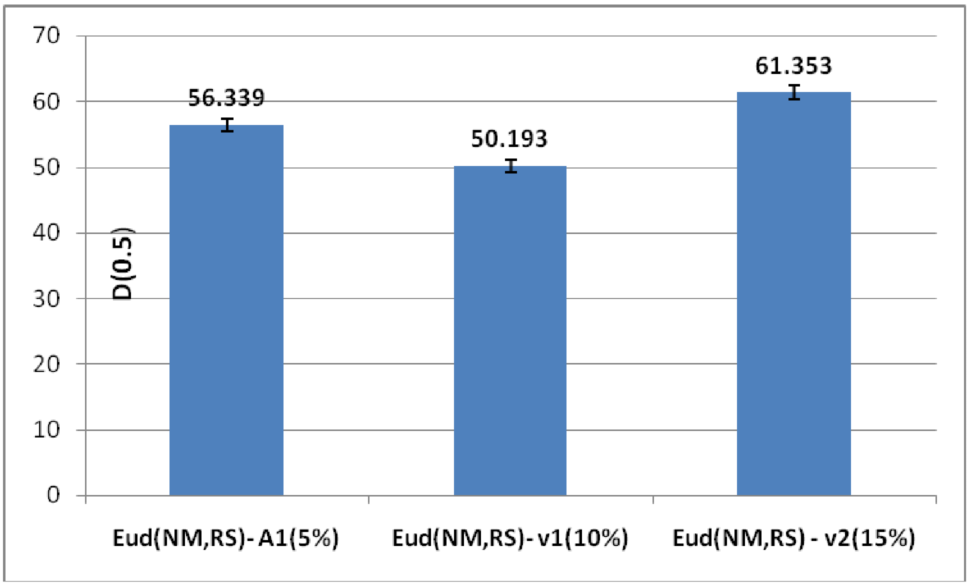


Figure (4): Effect of the internal phase concentration on the particle size.

Concerning differences in the Monodispersity index. (δ) (Table 7); the value was significant in case of SLS which showed significant decrease in δ, as the concentration of the surfactant increases, the particles would become more monodispersed, in other words, the particles would have narrower distribution. In the case of Tween 20, an increase in its concentration resulted in broader distribution. For Lutrol F68, there was an insignificant change in the δ.

Table (6): δ values as a function of surfactant content.

Formula code	δ ± standard deviation
SLS-1(0.12%)	9.43 ± 3.33
SLS-2(0.23%)	2.856 ± 0.886
SLS-3(0.35%)	0.679 ± 0.213
SLS-4(0.45%)	3.6 ± 1.17
TW 20 - A1 (0.35%)	7.09 ± 2.04
TW 20 - A2(0.45%)	8.14 ± 3.09
LT - F68 -A1(0.35%)	2.64 ± 0.831
LT - F68 -A2(0.45%)	2.983 ± 0.883

Table (7): δ values as function of surfactant type.

formula code	δ ± standard deviation
SLS-A4	3.62 ± 1.17
LT - F68 - A2	2.98 ±0.883
TW 20 - A2	8.14 ±2.04

1.1.3 Effect of the temperature on the dispersed phase on the particle size.

The influence of temperature on the particle size was evaluated; the temperature was changed from 25 °C to 40°C, the particles become larger in size as it appears in figure (5). This could be explained by the work of Freitas et al. (2004), in which elevation of the temperature lead to rapid evaporation of the organic solvent that lead to the formation of particles coarser and larger in their nature.

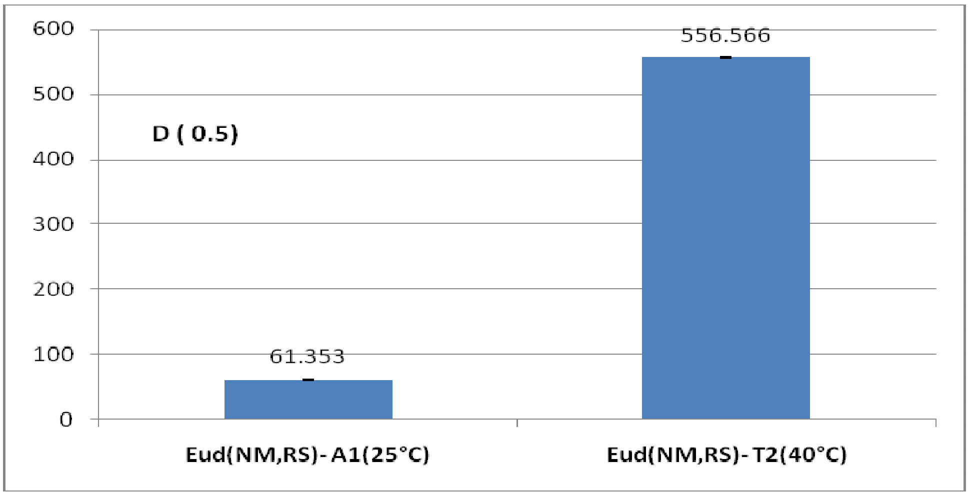


Figure (5): Effect of elevating the tempresure from 25°C to 40°C on the particle size.

1.2 Loading efficiency.

The loading capacity of the system was evaluated. It is important to evaluate the capacity of the microparticles to carry the drug. Authors like Andre-Abrant noticed that the encapsulation efficiency increase by increasing the quantity of the drug. (André-Abrant et al., 2001). They assumed that as the continuous phase increases this will lead to the loss of the drug in it, accordingly further increase in the drug content may be required, in order to increase the percentage of the drug encapsulated. The results of the experiments in relation to the evaluation of drug content are discussed below.

1.2.1 The effect of the surfactant type and concentration on the loading efficiency:

Different surfactant has been evaluated (SLS, Tween 20, Lutrol F68) for their effect on the drug content, which is expressed as percentage of drug encapsulated, calculated as the percentage of the actual amount from the theoretical amount. The results for the microparticles stabilized by SLS were as the following:

Table (8): Encapsulation efficiencies of the microparticles prepared by SLS.

Formula code	Encapsulation efficiency (%)
SLS - A1	80.10%
SLS - A2	80.70%
SLS - A3	80.69%
Eud (NM,RS) –A2	70.88%

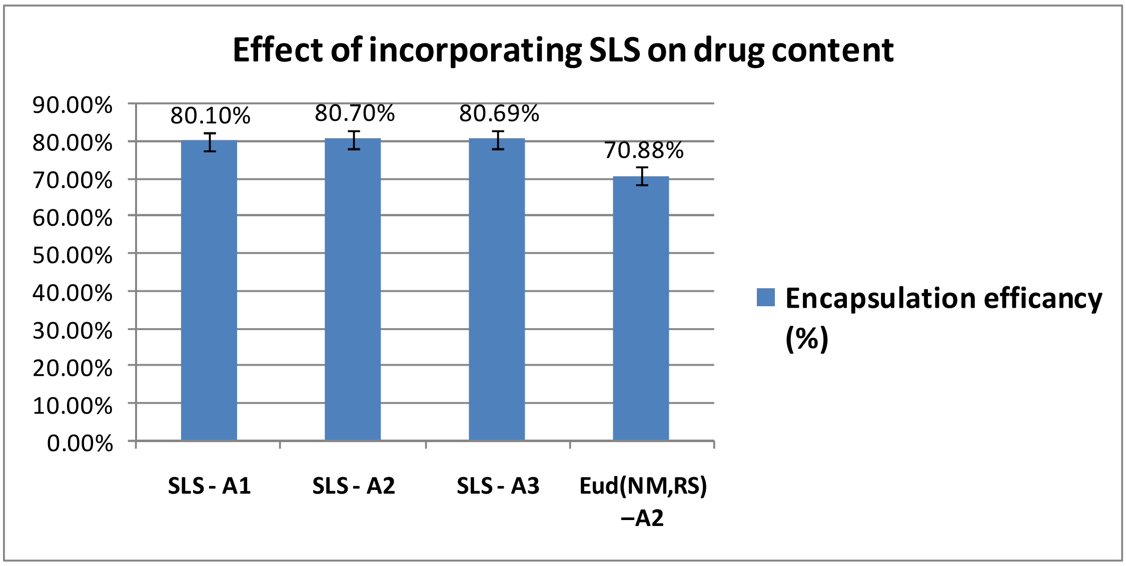


Figure (6): Encapsulation efficiencies in microparticles stabilized by SLS as surfactant.

It is noticed from the previous results for SLS result that there was a significant difference around 10 % in the amount of the theophylline encapsulated between the formulations that contained SLS compared to the ones without SLS as shown in figure 6. No effect on the encapsulation efficiency was observed for increasing the percentage of SLS.

The results for the microparticles stabilized by Tween 20 are as the following:

Table (9): Encapsulation efficiencies of the microparticles stabilized by Tween 20.

Formula code	Encapsulation efficiency (%)
TW 20 - A1	80.10%
TW 20 - A2	92.20%
Eud (NM,RS) –A2	70.88%

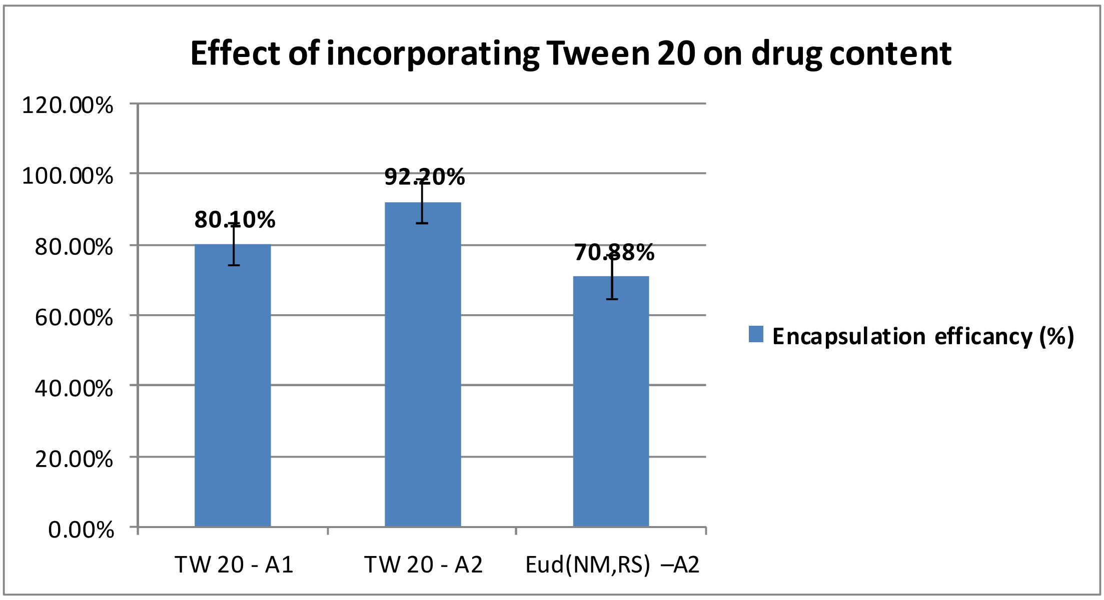


Figure (7): Encapsulation efficiencies in microparticles stabilized by Tween 20 as surfactant.

It is noticed that for theophylline - loaded microparticles stabilized by Tween 20, there was a difference between the formulations with tween compared to the ones without it. Also, it was noted that as the concentration of the surfactant increased, the content of the drug increased also, this appeared significantly in the formula TW 20 – A2 which had a more than 20% increase in encapsulation compare to formula Eud(NM,RS) –A2 that contains 0% surfactant.

The effect of Lutrol F 68 on drug release was evaluated and the results are as the following:

Table (10): Encapsulation efficiencies of the microparticales stabilized by Lutrol F 68.

Formula code	Encapsulation efficancy (%)
LT - F68 - A1	80.40%
LT - F68 – A2	96.96%
Eud(NM,RS) –A2	70.88%

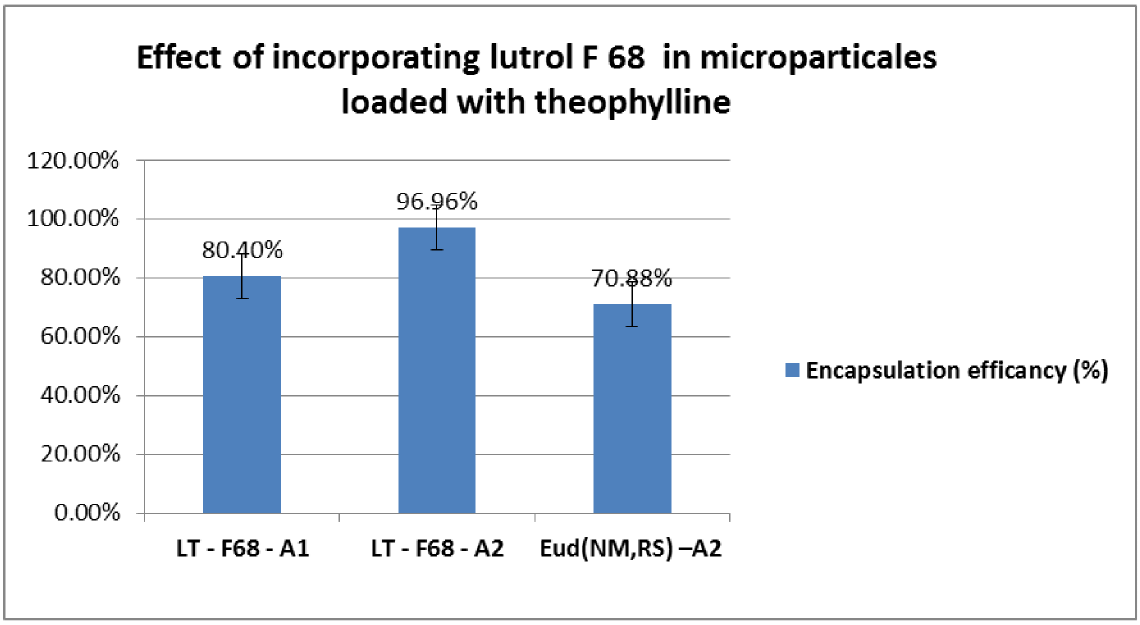


Figure (8): Encapsulation efficiencies in microparticles stabilized by Tween 20 as surfactant.

From the figures (7, 8) we can find that Lutrol has the same effect as Tween, in which, increasing the concentration of the surfactant increased the encapsulation efficiency. The increase was around 26%.

Comparing the previous surfactants and the amount of the drug encapsulated, we can conclude that surfactants Lutrol – F68 and Tween 20, were the most efficient in Encapsulating drugs, when it's compared to SLS that showed only by 10% when compared to others.

1.2.2 Effect of elevating the temperature on drug content.

The effect of temperature on the drug content was evaluated. The results as shown in table 10 showed that elevating the temperature had a negative effect on the encapsulation efficiency which led to a decrease in the drug loading. This can be explained by the evaporation rate of the solvent which didn't allow a chance for the polymer to deposit at the surface of the solid particles (drug). Accordingly, the encapsulation efficiency decreases (Freitas et al., 2004).

Table (10): Encapsulation efficiencies of the microparticles prepared under 40° C.

Formula code	Encapsulation efficiency (%)
Eud(NM,RS) –T1	65.07%
Eud(NM,RS) –T2	81.70%
Eud(NM,RS) –T3	83.70%
Eud(NM,RS) –A2	70.88%

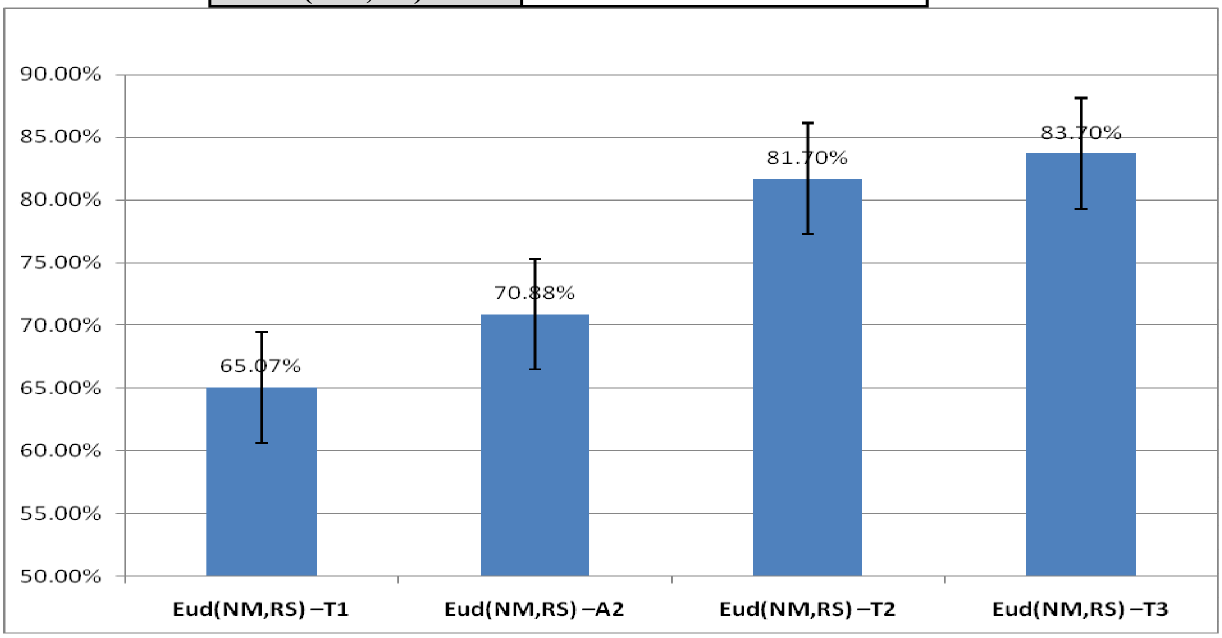


Figure (9): Encapsulation efficiencies in microparticles prepared under 40° C.

1.2.3 Effect of incorporating Eudragit NM in the formula.

Eudragit NM 30D present as 30% solid partials that is added to Eudragit RL 30 D polymer in order to control the release of theophylline from the microparticles. Both polymers are neutral, PH independent, and Eudragit NM 30D is considered to be medium in its permeability (Evonik® company specification, Germany).

Table (11): Encapsulation efficacies of theophylline – loaded microparticles under the effect of addition of different relative proportions of Eudragit NM.

Formula code	Encapsulation efficiency (%)
Eud(NM,RS) –A1	60.9%
Eud(NM,RS) –A2	70.0%
Eud(NM,RS) –A 3	80.8%

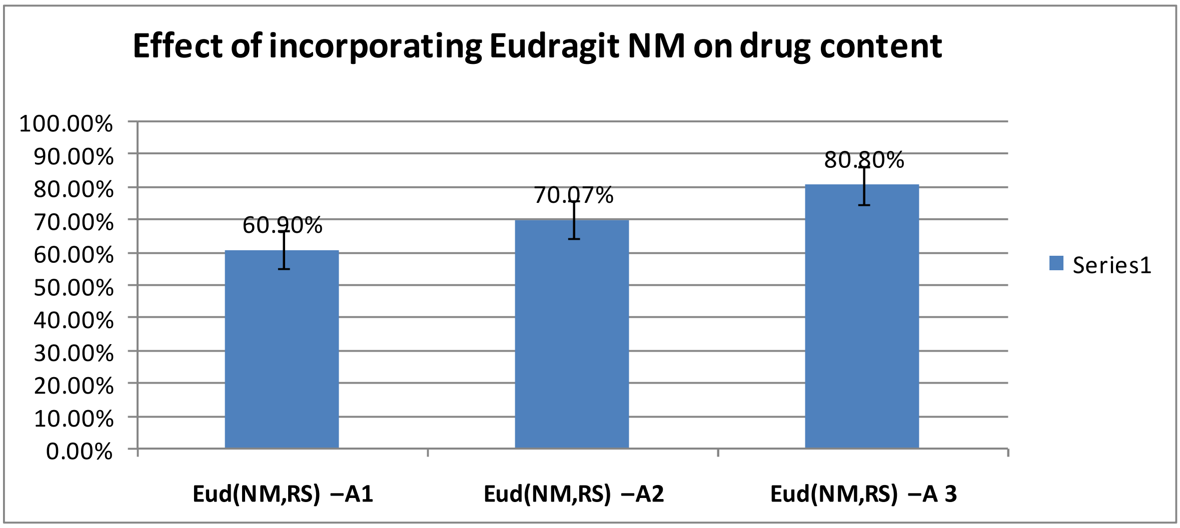


Figure (10): Encapsulation efficiencies in microparticles prepared by addition of different relative proportions of Eudragit NM.

It appears that by the addition of the polymer to the formula led to an increase in the encapsulation efficacies, as shown in figure 10 and table 11.

1.3 In – vitro release:

1.3.1 Effect of the surfactant type and content on in vitro release behavior of theophylline loaded microparticles.

As shown in figures (11, 12, 13 and 14), dissolution profiles of the theophylline loaded microparticles obtained from using Tween 20, Lutrol F68 and SLS with high HLB values provided in table (12) are satisfactory and thus support the assumption, that these hydrophilic surfactants are thought to decrease the interfacial tension between the microparticles and the dissolution media by acting as wetting agents, thus facilitating the diffusion of media through the polymeric matrix of the particles.

Calculations of the similarity factor revealed the difference between the dissolution profiles ($F_{2\ (Eud\ (NM,\ RS)\ -\ A1,\ SLS\ –\ A4)}$, $F_{2\ TW\ 20-A1,\ TW\ 20-\ A2}$, $F_{2\ LT\ –F6\ –\ A1,\ LT\ –F6\ –\ A2)}$) are 48.6, 48.7 and 49.05 respectively.

It was noticed that the microparticles stabilized by different types of surfactants at 0.4 % (w/v) concentrations represented at figure (13), that the ones that are emulsified by Lutrol F68 and Tween 20 showed the highest release levels, which is nearly close to each other , while the one that is stabilized by SLS showed reduced release behavior.

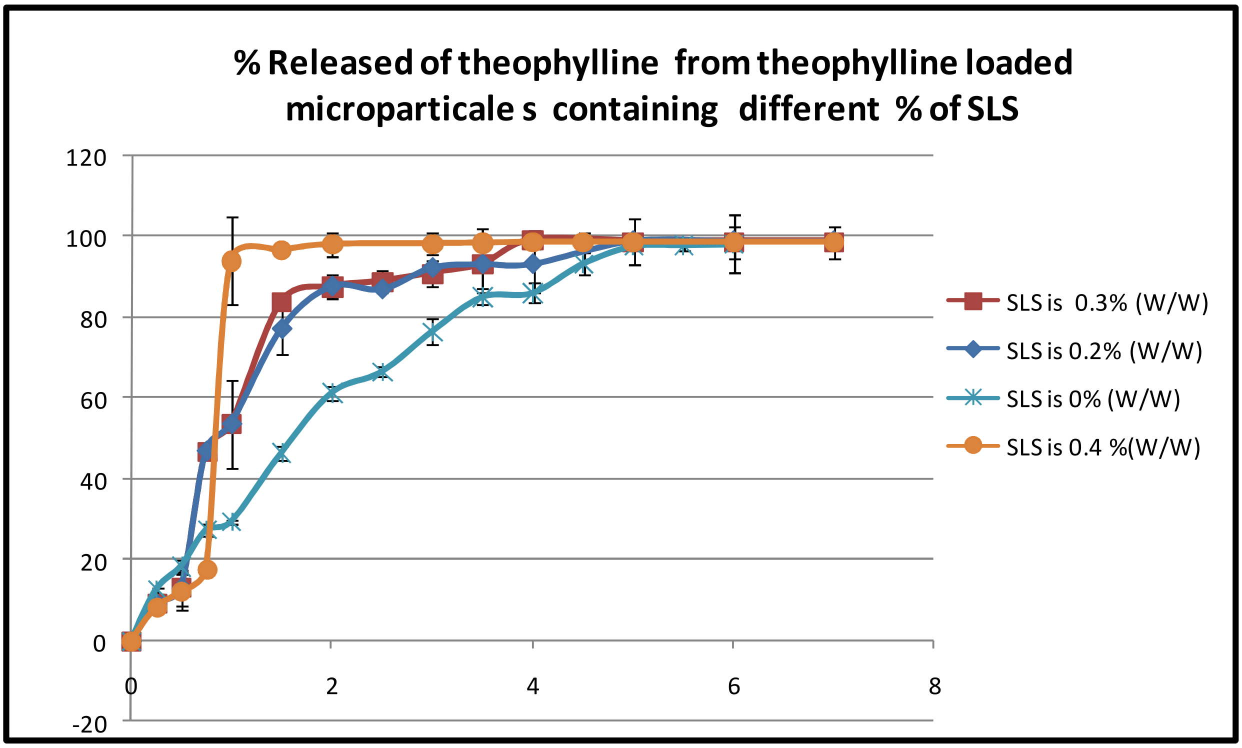


Figure (11): Dissolution profiles of theophylline – loaded microparticales containing different % of SLS.

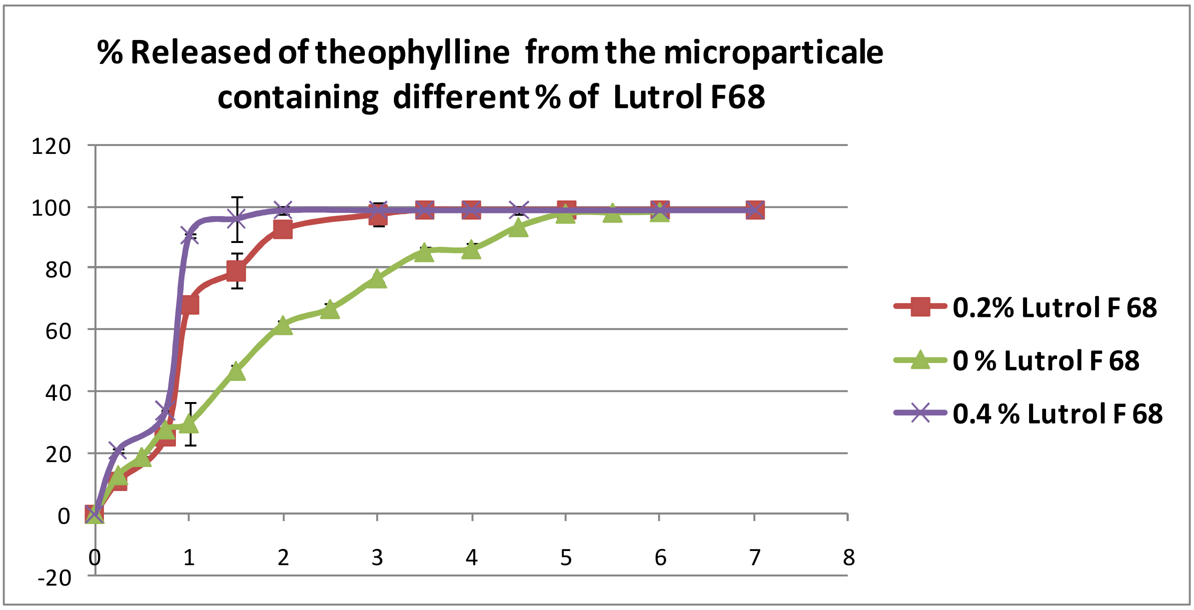


Figure (12): Dissolution profiles of theophylline – loaded microparticles containing different % of Lutrol F 68.

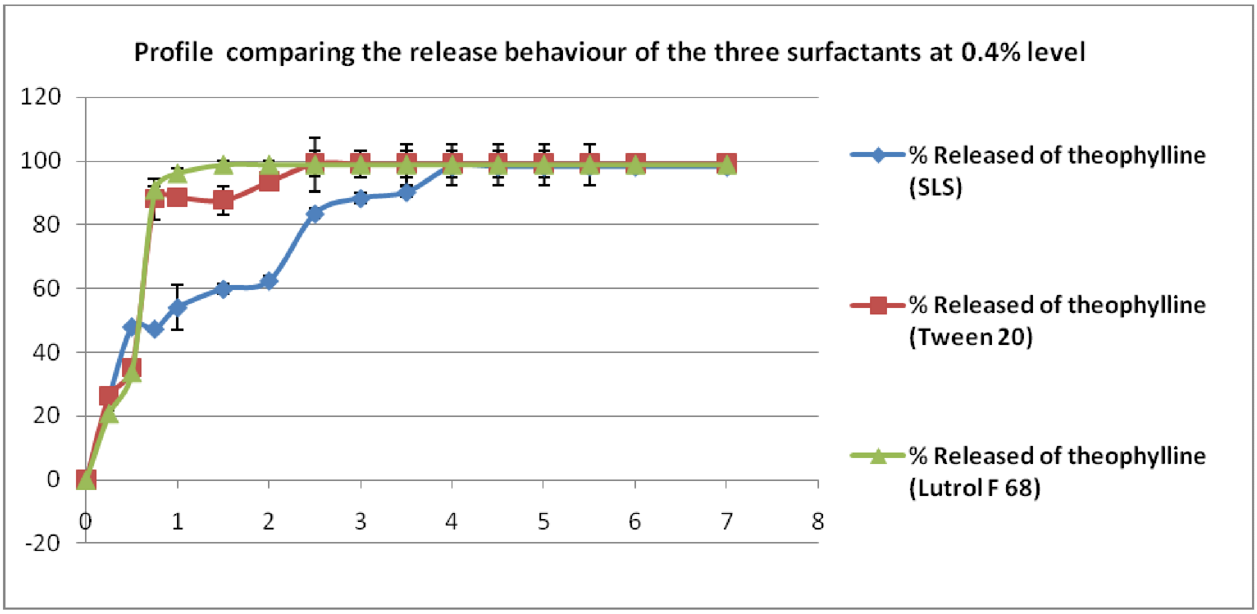


Figure (13): Dissolution profile comparing release behavior of the three surfactants used at 0.4% level.

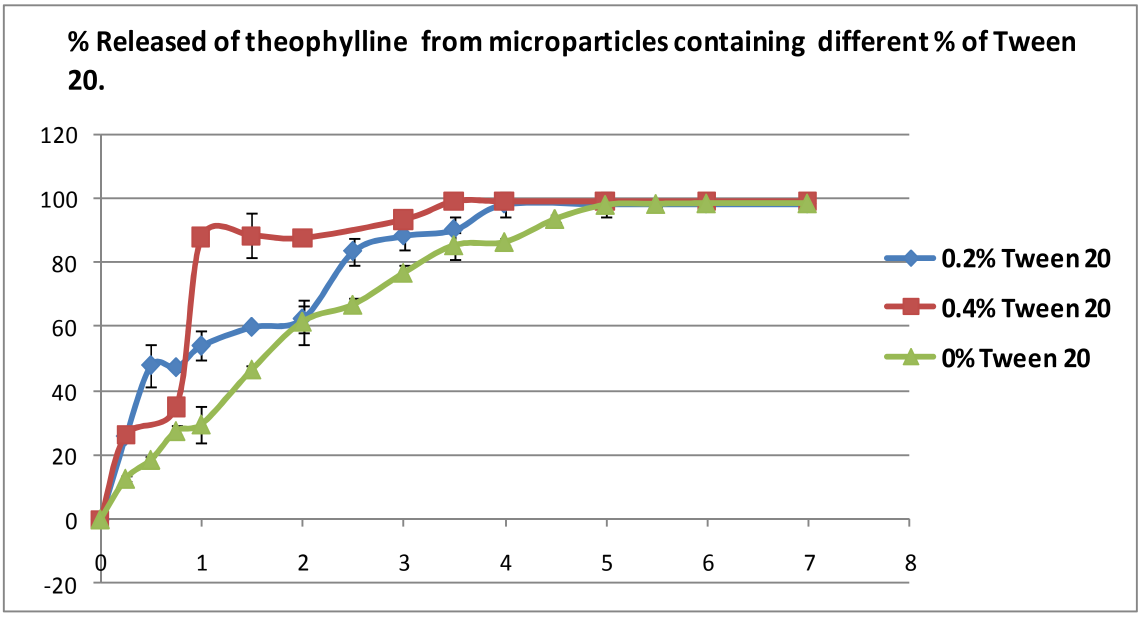


Figure (14): Dissolution profiles of theophylline – loaded microparticles containing different % of Tween 20.

Table (12): HLB values of the surfactants used in preparing theophylline – loaded microparticales.

Surfactant type	HLB value
• **SLS**	40
• **Tween 20**	16.7
• **Lutrol F 68**	28

1.3.2 Effect of the drug content on the release behavior of theophylline - loaded microparticles.

The theophylline loaded microparticales are prepared at different concentration levels ranging from 5%, 15% and 25% of polymer weight respectively.

It was noticed from the figure 15 that as the drug content increased, the percentage of release increased; the same results were also obtained in a study performed by (André-Abrant et al., 2001).

Microspheres with high drug loading are more porous and have more irregular shapes. The over porous surface is responsible for the drug loss accordingly, due to the shrinkage of the polymer, while the drug content stays the same so the drug would appear at the surface of the particles (Witschi and Doelker, 1998).

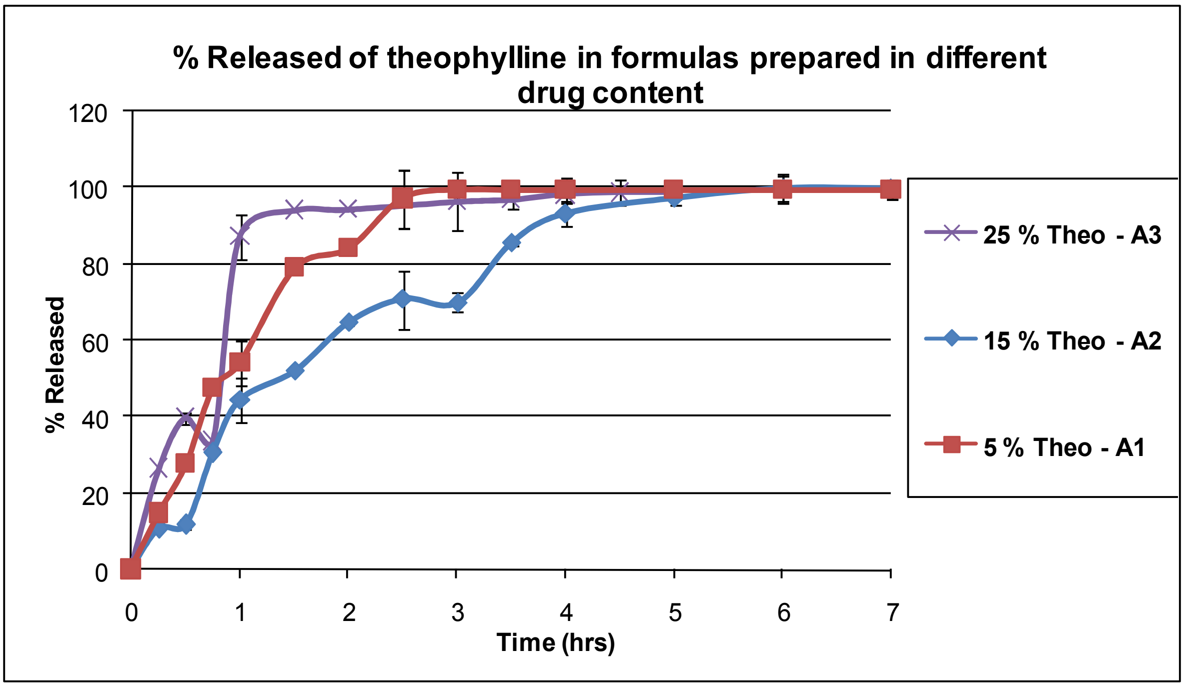


Figure (15): Dissolution profiles of theophylline – loaded microparticles containing different % of theophylline.

1.3.3 Effect of volume fraction of the dispersed phases to continuous phase.

The viscosity of the internal phase was changed by changing the volume of acetone to produce 5, 10 and 15% (w/w) polymeric solution by using 119.9, 56.8and 42.4 mLs of acetone respectively. The volume of water was changed in order to maintain constant internal phase to external phase percent of 33.3% for optimum stability of the emulsion formed.

It was noticed from the release behavior of the microparticles in figure 12, that upon increasing the viscosity of the internal phase the release from the particles reduces and the encapsulation efficiency increases. Figures 15, 16 and 17 show an increase in the encapsulation efficiencies upon increasing the viscosity of the internal phase at different ratios of Eudragit RS to Eudragit NM. This could be supported by the work Yang et al., (2000a), a higher polymer (ethyl cellulose) concentration resulted in higher drug

(aspirin) encapsulation, also confirmed by the work of André- Abrant et al., (2001), when ethyl benzoate is encapsulated by ethyl cellulose, the resulted microspheres were smooth in their surface with large particle size that led to decrease in the dissolution rate accordingly; the release of the drug reduces, this could be proved by the calculated similarity factor for the formulas presented at figure 16 at ($F_{2(Eud(NM,RS) - A1,\ Eud(NM,RS) - V1)}$, $F_{2(Eud(NM,RS) - A1,\ Eud(NM,RS) - V2}$ $F_{2(Eud(NM,RS) - V1,\ Eud(NM,RS) - V2)}$) are 49, 48.5 and 48.6, respectively.

The release behavior of the microparticles at different ratio of Eudragit RS to Eudragit NM was assessed at different internal phase viscosities. It was noticed that the release was less.

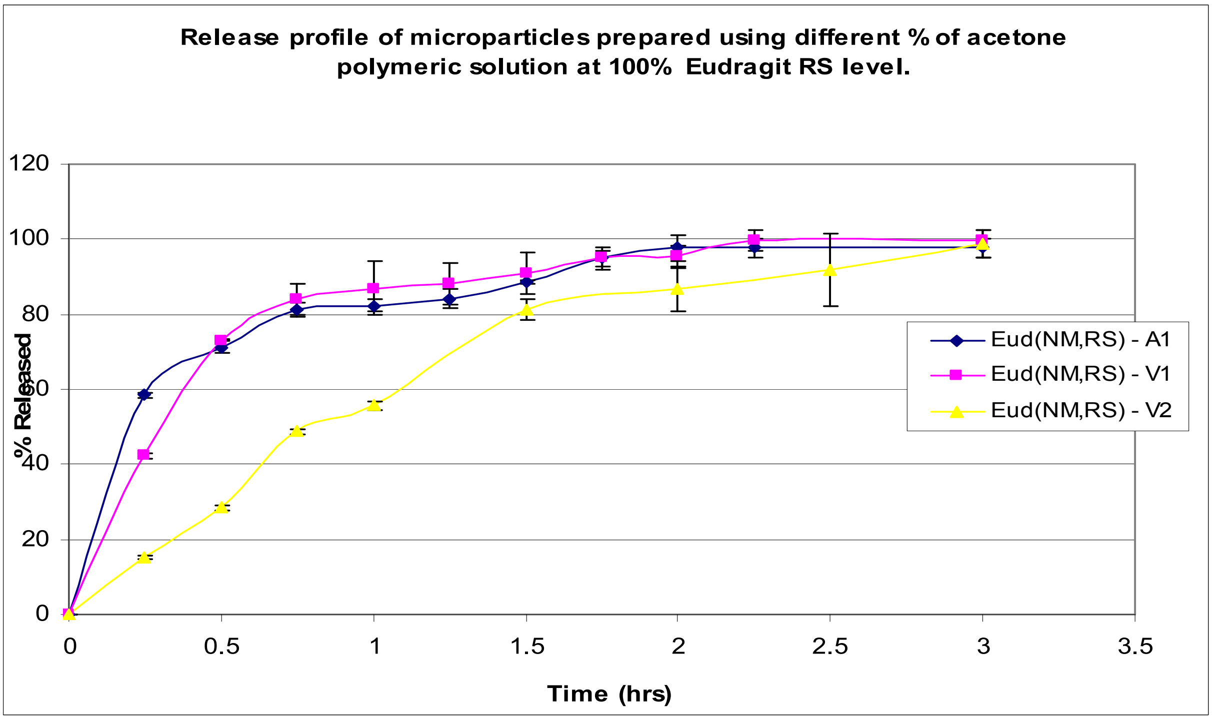


Figure (16): Dissolution profiles of theophylline – loaded Microparticles containing different % of acetone polymeric solution at 100 % Eudragit RS levels.

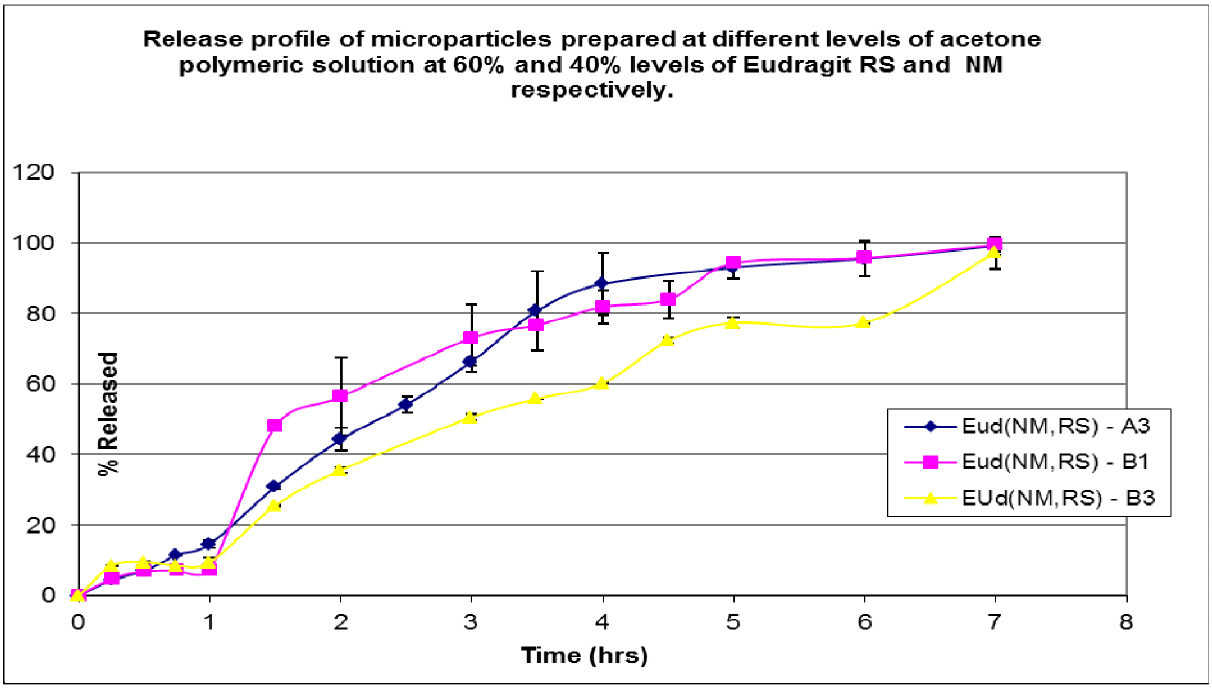


Figure (17): Dissolution profiles of theophylline – loaded Microparticles containing different % of acetone polymeric solution at 60 % Eudragit RS levels.

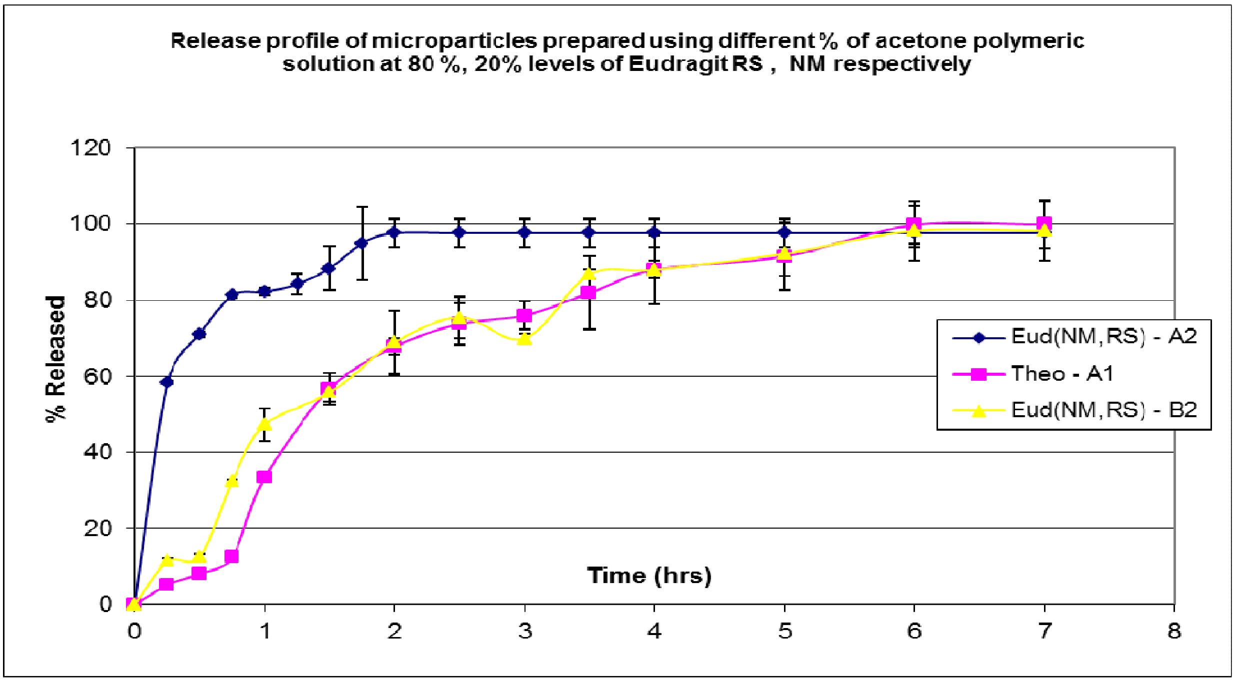


Figure (18): Dissolution profiles of theophylline – loaded Microparticles containing different % of acetone polymeric solution at 80% Eudragit RS levels.

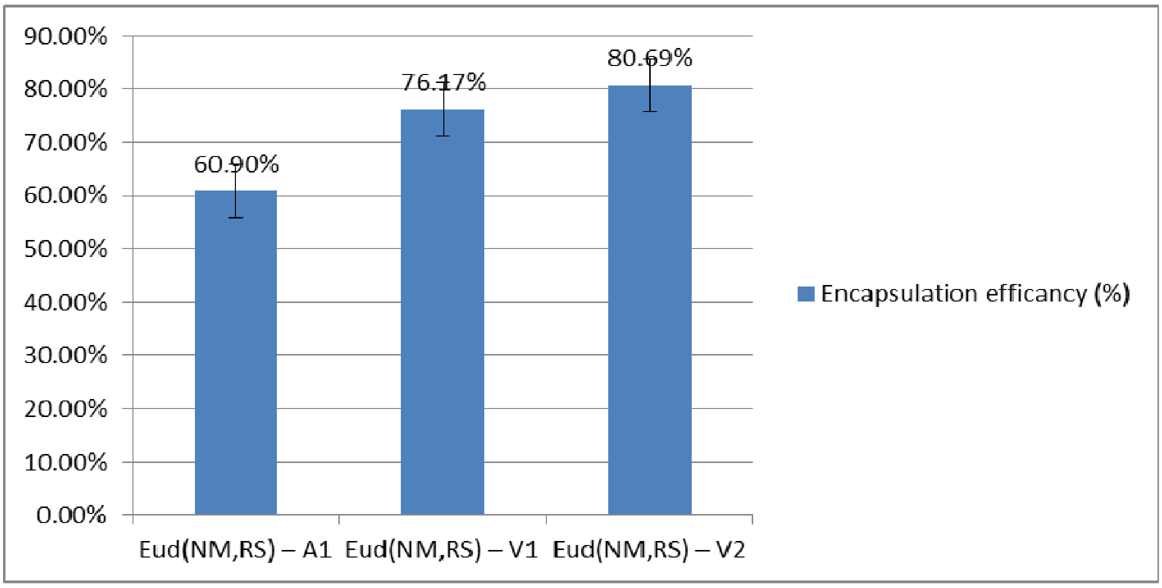


Figure (19): Encapsulation efficacies of theophylline – loaded Microparticales containing different % of acetone polymeric solution at 100% Eudragit RS level.

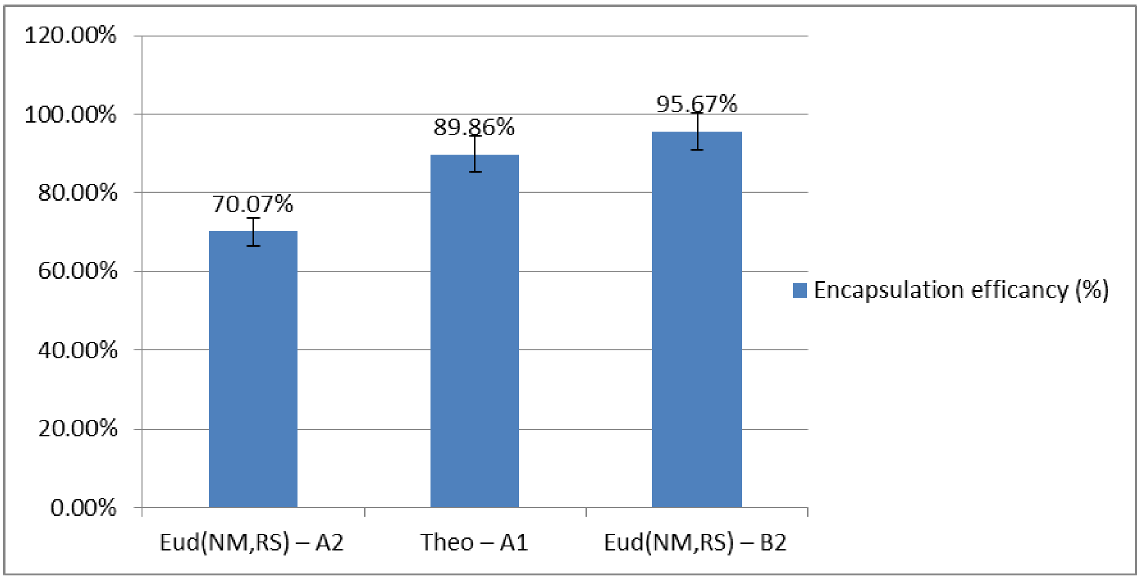


Figure (20): Encapsulation efficacies of theophylline – loaded Microparticales containing different % of acetone polymeric solution at 80% Eudragit RS level.

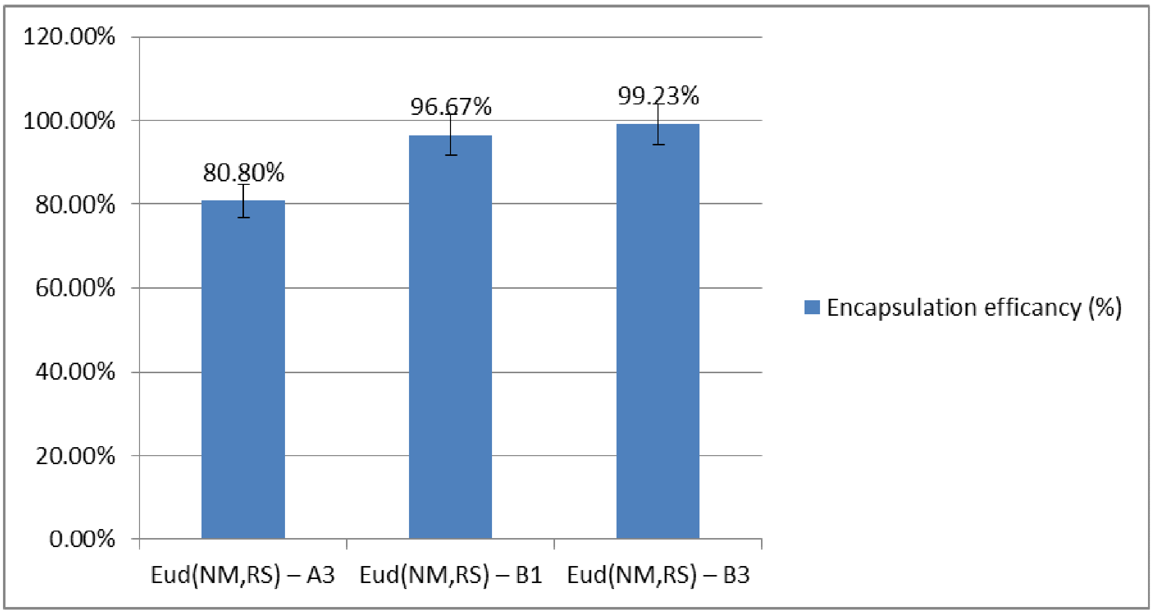


Figure (21): Encapsulation efficacies of theophylline – loaded Microparticales containing different % of acetone polymeric solution at 60% Eudragit RS level.

1.4 Thermal analysis:

Thermal behavior of theophylline - loaded microparticles prepared at several procedure variables including type and level of surfactant incorporated. E.g. (Tween 20 and Lutrol F68), different theophylline percentages, different polymeric solution concentrations of the internal phase, different ratios of Eudragit RS to Eudragit NM and at elevated temperature (40 °C), to facilitate the evaporation of the organic phase, were assessed .

Theophylline normally shows a single endothermic peak at 274°C and normalized enthalpy of - 168.5 mJ/mg; to its melting and Eudragit NM exhibit a main endothermic peak at 110°C and enthalpy of – 79.66 mJ/mg corresponding to its melting point.

Eudragit RS exhibits a main endothermic peak at 375°C and enthalpy of 57.49 mJ/mg, corresponding to its melting point. Pluronic F68 displays two endothermic peaks; the

first represents its melting at 58.64 °C and an enthalpy of – 113.4 mJ/mg and second small peak at 71.77 °C, which stems from melting of impurities.

DSC thermograms (22, 23, 24 and 25) at different procedure variables imply that theophylline is well dispersed through the polymeric matrices of the particles. The absence of the drug melting point upon heating could be explained by the formation of solid solution between the drug and the polymers. This phenomenon was studies by HaJimekonno et al., (2006). They concluded that drug was capable of interaction with the polymer (HPMC) to form a molecular dispersion.

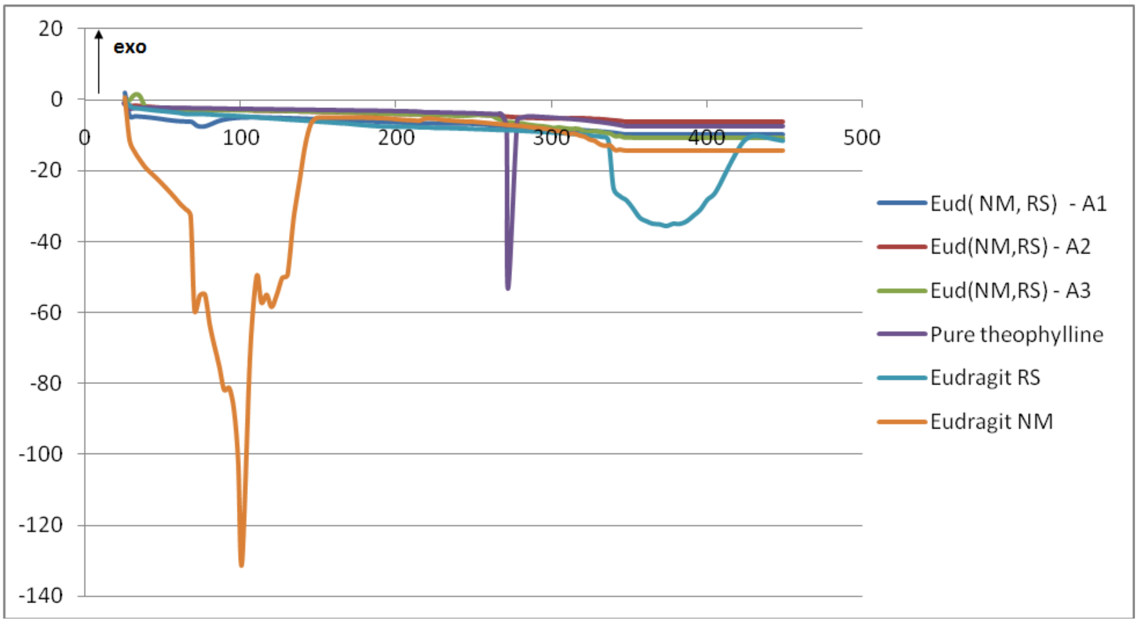


Figure (22): DSC thermograms of theophylline – loaded microparticales containing different % of Eudragit NM.

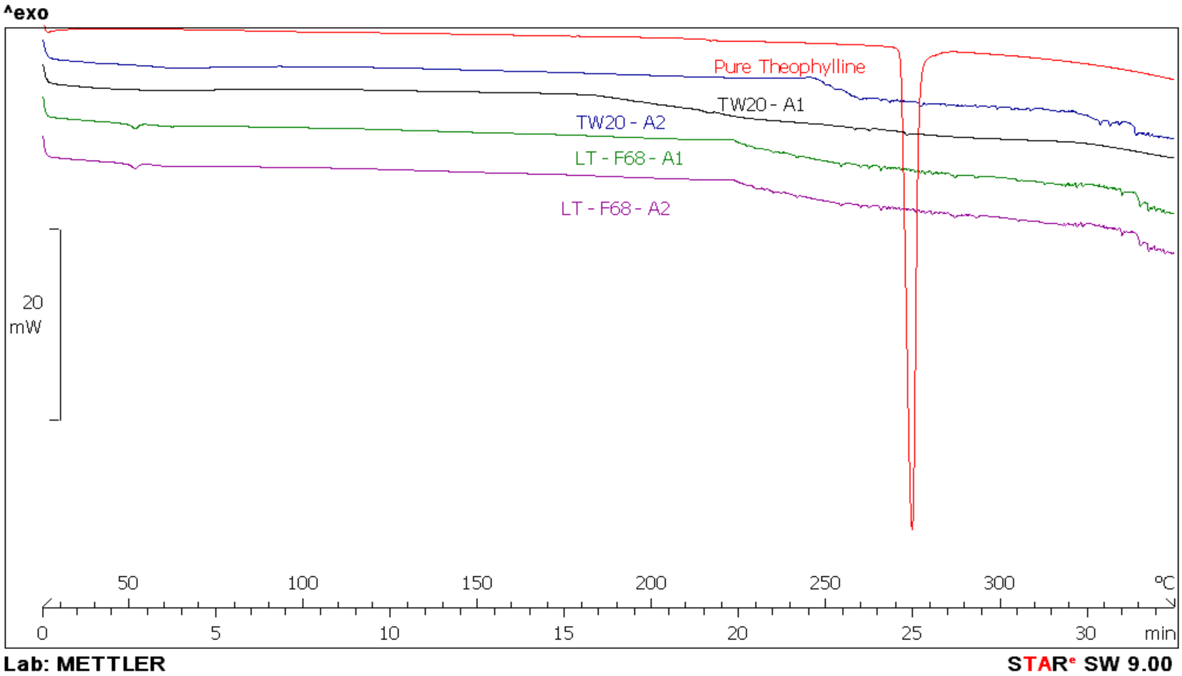


Figure (23): DSC thermograms of theophylline – loaded microparticales stabilized by different % of surfactants (Tween 20, Lutrol F68).

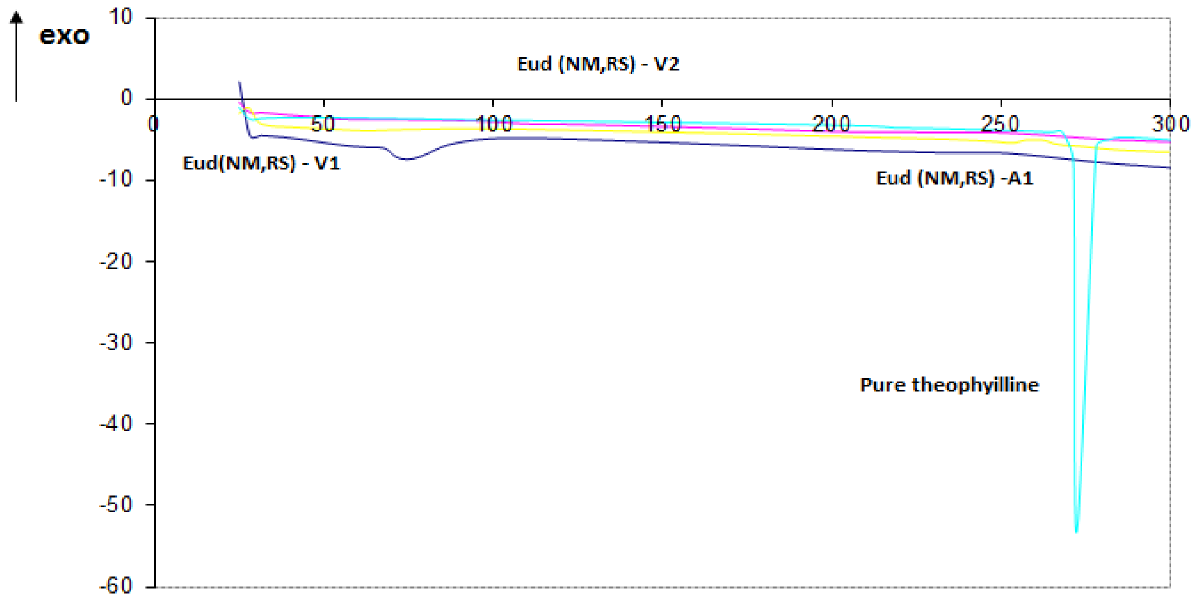


Figure (24): DSC thermograms of theophylline – loaded microparticales containing different % theophylline.

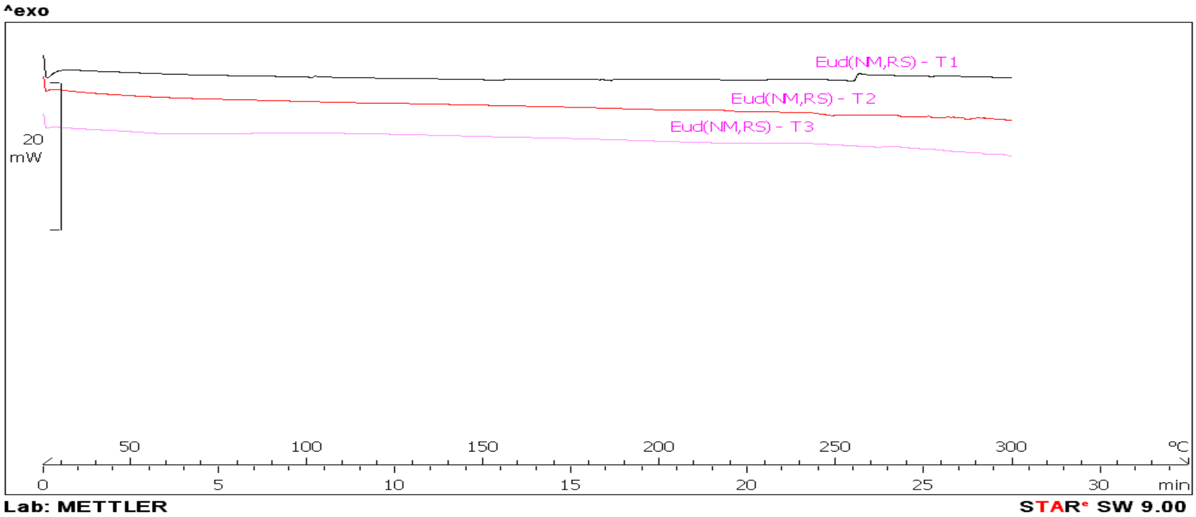


Figure (25): DSC thermograms of theophylline – loaded microparticales containing different % of Eudragit NM prepared under elevated Temperature 40C°.

1.5Mathematical modeling of the release profiles:

In order to clarify the mechanism of theophylline release from the prepared microparticles, the following release models were considered and assessed by regression analysis (R2 value). The obtained parameters were summarized in table (11).

1. Higuchi square root of time model:

This model assumes that the drug release is attained by the diffusion of the drug through an intact matrix (Paker – legges and neau, 2008). This model is presented by the following.

$$\mathbf{M_t / M_\infty = k\, t^{1/2}}$$

Where M_t / M_∞ donate the drug fraction release at time t, K and n are the rate constants and the kinetic exponent of the release, respectively. **Korsmeyer – Pappas model.**

The following expression for the analysis is applied:

$$\mathbf{M_t / M_\infty = k\, t^{1/2}}$$

Where $M_t / M_{\infty \text{ denotes}}$ the drug fraction release at t. K and n are the rate constant and kinetic exponent of release, respectively The data analysis was limited to 60% release. This model differs from the previous one in that the exponent n is not fixed at 0.5; the value of n defines the mechanism of the release process.

When n equals 0.5, fickian diffusion is suggested release mechanism and when n value is between 0.5 – 1, the suggested release mechanism is non- Fickian diffusion or Fickian diffusion and at least one other release mechanism (Paker – legges and neau, 2008). The data analysis was limited to 60% release.

Although fitting the data of microparticles to Korsmeyer – Peppas model resulted in high values of the exponent n indicating disintegration and erosion of these microparticles in dissolution media , this reading could be misleading interpretation of the data may occurred. This attributed to the aggregation of the microparticles in the dissolution media leading to misintrubutation of the release mechanism.

Table (13): Parameter values from model fitting to the release data of the investigated microparticales formulas.

Formula code	Higuchi model		Korsmeyer – Peppas model		
	K(h^{-1})	R^2	K (h^{-1})	n	R^2
Eud (NM,RS) – A1	0.8312 ± 0.02	0.9401	0.839± 0.01	*0.517*	0.881
Eud (NM,RS) – A2	0.6346 ± 0.01	0.9679	0.398± 0.01	*0.760*	0.99
Eud (NM,RS) – A3	0.6346 ± 0.04	0.9679	0.246± 0.02	1.357	0.586
Eud (NM,RS) – V1	0.6346 ±0.04	0.9679	0.147± 0.01	0.229	1
Theo – A1	0.2384 ±0. 3	0.9364	0.269±0.04	1.369	0.94
Eud (NM,RS) – B1	0.165 ± 0.02	0.8814	0.167±0.04	1.242	0.736
Eud (NM,RS) – V2	0.541 ± 0.01	0.978	0.588±0.05	0.979	0.986
Eud (NM,RS) – B2	1.1999 ± 0.04	0.8814	0.167±0.05	1.242	0.737
Eud (NM,RS) – B3	0.8471 ± 0.03	0.8359	0.183±0.02	0.828	0.758
Theo – A2	0.627 ± 0.02	0.6266	0.183±0.02	0.828	0.758
Theo – A3	0.1636 ± 0.32	0.952	0.379±0.01	0.539	0.61
Eud (NM,RS) – T1	0.468 ± 0.43	0.9657	0.371±0.07	0.181	1
Eud (NM,RS) – T2	0.24 ± 0.05	0.8205	0.183±0.03	0.828	0.758
Eud (NM,RS) – T3	0.113±0.02	0.8603	0.185±0.02	0.847	0.835
SLS – A1	0.8204±0.01	0.9427	0.1096±0.04	0.763	0.854
SLS – A2	0.416 ±0.04	0.8917	0.363±0.03	0.92	0.931
SLS – A3	0.112 ± 0.03	0.8483	0.4602±0.03	0.855	0.897
SLS – A4	0.21086±0.04	0.982	0.1096±0.12	0.763	0.854
TW 20 – A1	0.5312 ± 0.02	0.922	0.393±0.032	0.693	0.863
TW 20 – A2	0.621 ± 0.03	0.62	0.265±0.05	0.665	1
LT – F68 –A1	0.5034 ± 0.04	0.5034	1.18±0.067	1.187	0.873
LT – F68 – A2	0.382 ±0.01	0.382	0.436±0.05	0.459	1

Conclusion

Theophylline - loaded microparticles were prepared using the solvent evaporation technique these microparticles were prepared using different procedure variables including temperature (25 °C and 40 °C), volume fraction of the dispersed phase to the continuous phase (5, 10, and 15%) and quantities of theophylline in the dispersed phase (15, 25 and 5%) of the polymer weight respectively. These microparticales were assessed in terms of their release behaviors, particles size and loading efficacies.

It was noticed that as the fraction of the Eudragit NM increases the encapsulation efficacy increases, also the incorporation of surfactants Tween20 and Lutrol F 68 was capable to increase the percentage of drug encapsulated by 21.32% , when compared to SLS. Temperature was capable to decrease the encapsulation efficacy by 10%, when it is compared to the one that is prepared at room temperature.

The particle size of the microparticles prepared was analyzed under the influence of the surfactant type and concentration, it was noticed that the addition of poloxamer (Lutrol F68) leads to decrease in the particle size when it is compared to the size of mic particles stabilized by SLS, which could be attributed to the Zeta potential around the particle that to particle aggregation.

The percentage of the dispersed phase to the continuous phase was assessed as the concentration of the dispersed phase increases a slight decrease in the particle size was noticed, once the volume fraction changes from 5 % (W/V) to 10 % (w/v), when the concentration of the internal phase increases and approaches 15 % (W/V), the size of the dispersed microspheres increases, accordingly the size of the particle increases.

The effect of temperature on the particle size was evaluated once the temperature is changed from 25°C to 40°C, the particles become larger in size.

The release data of microparticles was fitted according to Korsmeyer – Peppas model which resulted in high values of the exponent n indicating disintegration and erosion of these microparticles in dissolution media, this reading could be misleading interpretation of the data. This could be attributed to the aggregation of the microparticles in the dissolution media leading to misinterpretation of the data of the release mechanism.

References

André-Abrant, A., Taverdet, J.-L., Jay, J., 2001. Microencapsulation via solvant evaporation technique.**Eur. Polym. J.** 37, 955–967.

Aso, Y., Yoshioka, S., Li Wan Po, A., Terao, T., (1994). Effect of temperature on mechanisms of drug release and matrix degradation of poly (-lactide) microspheres. **J. Contr. Rel.** 31, 33–39.

Azevedo, A.F., Galhardas, J., Cunha, A., Cruz, P., Goncalves, L.M.D., Almeida, A.J., 2006.Microencapsulation of *Streptococcus equi*antigens in biodegradable microspheres and preliminary immunization studies**. Eur. J. Pharm. Biopharma**. 64, 131–137.

Bahl, Y., Sah, H.,(2000). Dynamic changes in size distribution of emulsion droplets during ethyl acetate-based microencapsulation process. **AAPS Pharm. Sci. Technol**., 1.

Banker GS. The new water based colloidal dispersions. **Pharm Technol** (1981); 5(4):12–19.

Berchane, N.S., Jebrail, F.F., Carson, K.H., Rice-Ficht, A.C., Andrews, M.J., (2006). About mean diameter and size distributions of poly (lactide-co-glycolide) (PLG) microspheres. **J. Microencap**. 23, 539–552.

Calderbank, P.H., (1958). Physical rate processes in industrial fermentation. Part I: The interfacial area in gas-liquid contacting with mechanical agitation. **Trans. Inst. Chem. Eng**. 36, 443–463.

Chulia, D., Deleuil, M., Pourcelot, Y., (1994). Powder Technology and Pharmaceutical Processes. **Elsevier Science Publishing Company, New York.**

Chung, T.-W., Huang, Y.-Y., Liu, Y.-Z., (2001). Effects of the rate of solvent evaporation on the characteristics of drug loaded PLLA and PDLLA microspheres. **Int. J. Pharm**. 212, 161–169.

Dai, C., Wang, B., Zhao, H., (2005). Microencapsulation peptide and protein drugs. Delivery system. Colloids. Surf. B: Biointerf. 41, 117–120.

Fatome, M., Courteille, F., Laval, J.D., Roman, V.,(1987). Radio protective activity of ethylcellulose microspheres containing WR 2721, after oral administration. Int. J. Radiat. Biol. Relat. **Stud. Phys. Chem. Med**. 52, 21–29.

Feng, L., Qi, X.R., Zhou, X.J., Maitani, Y., Cong Wang, S., Jiang, Y., Nagai, T., (2006). Pharmaceutical and immunological evaluation of a single-dose hepatitis B vaccine using PLGA microspheres. J. Contr. Rel. 112, 35–42.

Freitas, S., Merkle, H.P., Gander, B., 2004. Microencapsulation by solvent extraction/evaporation: reviewing the state of the art of microsphere preparation Process technology. **J. Contr. Rel**. 102, 313–332.

Freytag, T., Dashevsky, A., Tillman, L., Hardee, G.E., Bodmeier, R., (2000).Improvement of the encapsulation efficiency of oligonuclleotide-containing biodegradable microspheres.**J. Contr. Rel**. 69, 197–207.

Furtado, S., Abramson, D., Simhkay, L., Wobbe kind, D., Mathiowitz, E., (2006),Subcutaneous delivery of insulin loaded poly (fumaric-co-sebacic anhydride) microspheres to type 1 diabetic rats. **Eur. J. Pharm. Biopharma**. 63, 229–236.

Gabor, F., Ertl, B., Wirth, M., Mallinger, R., (1999). Ketoprofen –poly (d,l-lactic-coglycolic acid) microspheres: influence of manufacturing parameters and type of polymer on the release characteristics. **J. Microencap**. 16, 1–12.

Herrmann, J., Bodmeier, R., (1998). Biodegradable somatostatin acetate containing microspheres prepared by various aqueous and non-aqueous solvent evaporation methods. **Eur. J. Pharm. Biopharma**. 45, 75–82.

Hinze, J., (1955). Fundamentals of the hydrodynamic mechanism of splitting in dispersion processes**. AIChE J**. 1, 289–295.

J. Contr. Rel. 47, 233–245.

Jalal, R., Nixon, J.R., (1990). Microencapsulation using poly (dl-lactic acid)I: effect of preparative variables on the microcapsule characteristics and release kinetics. **J.Microencap**. 7, 229–244.

Katchalski-Katzir E, Kramer DM. **J MolCatal B** (2000); 10:157–176. Bosch T, Wendler T. TherApher Dial (2004); 8:269–274.

Kumar, S., Kumar, R., Gandhi, K.S.,(1993). A simplified procedure for predicting *d*maxin stirred vessels **.Chem. Eng. Sci. 48**, 3092–3096.

Laila F. A.A., Chandran S., Multiparticulate Formulation approach to colon specific drug delivery current perspectives**, J. Pharm Pharm Sci**, 2006, 9(3): 327-338.

Li, X., Deng, X., Yuan, M., Xiong, C., Huang, Z., Zhang, Y., Jia, W., (1999a). Investigation on process parameters involved in preparation of poly-dl-lactide-poly (ethylene glycol) microspheres containing LeptospiraInterrogans antigens. **Int. J. Pharm**. 178, 245–25.

Li, X., Zhang, Y., Yan, R., Jia, W., Yuan, M., Deng, X., Huang, Z., (2000b). Influence of process parameters on the protein stability encapsulated in poly -dl- lactidepoly(ethylene glycol) microspheres. **J. Contr. Rel.** 68, 41–52.

Little, S.R., Lynn, D.M., Puram, S.V., Langer, R., (2005).Formulation and characterization of poly (beta amino ester) microparticles for genetic vaccine delivery. **J. Control Rel**. 107, 449–462.

Luan, X., Skupin, M., Siepmann, J., Bodmeier, R., (2006). Key parameter safe Acting the initial release (burst) and encapsulation efficiency of peptide containing poly(lactide-co-glycolide) microparticles. **Int. J. Pharm**. 324, 168–175.

Mana, Z., Pellequer, Y., Lamprecht, A., (2007).Oil-in-oil microencapsulation technique with an external perfluorohexane phase.**Int. J. Pharm**. 338, 231–237.

Mateovic, T., Kriznar, B., Bogataj, M., Mrhar, A.,(2002). The influence of stirring rate on biopharmaceutical properties of Eudragit RS microspheres **J. Microencap**. 19, 29–36.

Meinel, L., Illi, O.E., Zapf, J., Malfanti, M., Merkle, H.P., Gander, B., (2001). Stabilizing insulin next-like growth factor-I in poly(d,l-lactide-co-glycolide) microspheres**. J. Contr. Rel**. 70, 193–202.

Meng, F.T., Ma, G.H., Liu, Y.D., Qiu, W., Su, Z.G., 2004. Microencapsulation of bovine hemoglobin with high bio-activity and high entrapment efficiency using a W/O/W double emulsion technique. **Colloïdes Surf. B 33**, 177–183.

Miyazaki, Y., Onuki, Y., Yakou, S., Takayama, K., (2006).Effect of temperature-increaserate on drug release characteristics of dextran microspheres prepared by emulsion solvent evaporation process. **Int. J. Pharm**. 324, 144–151.

Petereit HU, Weisbrod W. Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers**. Eur J Pharma Biopharm.** (1999); 47:15–25.

Preparing Modified Release Multiparticulate Dosage Forms With Eudragit Polymers**, Pharma Polymers**, November 2002, 9:2-3

Sah, H., 1997.Microencapsulation techniques using ethyl acetate as a dispersed solvent: effects of its extraction rate on the characteristics of PLGA microspheres.

Shaji J., Chadawar V.,Talwalkar P., Multiparticulate Drug Delivery System, **The Indian Pharmacist**, June 2007, 6(60): 21-28.

Singh, M., Shirley, B., Bajwa, K., Samara, E., Hora, M., O'Hagan, D., (2001).Controlled release of recombinant insulin-like growth factor from a novel formulation of polylactide-co-glycolide microparticles. **J. Contr. Rel**. 70, 21–28.

Solomon B, Raviv O, Leibman E, Fleminger G. **J Chromatogr** (1992); 597:257–262.

Stallmann, H.P., Faber, C., Bronckers, A.L., Amerongen, A.V.N.,Wuisman, P.I., (2006). Invitro gentamicin release from commercially available calcium-phosphate bone substitutes influence of carrier type on duration of the release profile BMC. Musculoskelet.Disord.7, 18.

Takishima, J., Onishi, H.,Machida,Y., (2002). Prolonged intestinal absorption of cephradine with chitosan-coated ethylcellulose microparticles in rats**. Biol. Pharm. Bull**. 25, 1498–1502.

Tang E. S.K., Chan L.W, Heng P.W.S, Coating of Multiparticulates for Sustained Release, **Amer J Drug Delivery** 2005: 3(1): 17-28.

Turi EA, ed. Thermal Characterization of Polymeric Materials**. New York: Academic Press**, (1981).

Witschi, C., Doelker, E., (1998). Influence of the microencapsulation method and peptide loading on poly(lactic acid) and poly(lactic-co-glycolic acid) degradation during in vitro testing**. J. Contr. Rel. 51**, 327–341.

Yang, C.Y., Tsay, S.Y., Tsiang, R.C.C., (2000a).An enhanced process for encapsulating aspirin in ethylcellulose microcapsules by solvent evaporation in an O/W emulsion **.J. Microencap**. 17, 269–277.

Yang, Y.Y., Chung, T.S., Bai, X.L., Chan, W.K., (2000b).Effect of preparation conditions on morphology and release profiles of biodegradable polymeric microspheres containing protein fabricated by double-emulsion method. **Chem. Eng. Sci**. 55, 2223–2236.

Zhang H., Alsarra I.A., Neau S.H., An in vitro evaluation of a chitosan-containing multiparticulate system for macromolecule, **In J of Pharm**, 2002, 239(1):197-205.

Zhu, K.J., Lin, X., Yang, S., (1990).Preparation, characterization, and properties of polylactide(PLA)-poly(ethylene glycol) (PEG) copolymers: a potential drug carrier. **J. Appl. Polym**. Sci. 39, 1–9.

APPENDICES

- Drug release data of different theophylline microparticles data.
- Drug content data of different microparticles data.
- Particle size measurement data of different theophylline microparticles formulation.

Drug release data, Drug content data and particle size measurement data of different microparticles of different formulation.

Formula code	Drug release data			Drug content data					
	Time	Average drug released	Standard deviation	Average drug content (%)	Standard deviation	Average $D_{0.1(\mu m)}$	Average $D_{0.5}(\mu m)$	Standard deviation	Average $D_{0.9}(\mu m)$
Eud(NM,RS)-A1	0.5	71.16	0.316	60.9%	0.54	12.459	548.056	0.431	944.828
	1	82.26	1.123						
	1.5	88.42	5.6163						
	2	97.63	3.792						
Eud (NM, Rs) – A2	0.5	7.036	0.6166	70.88%	0.645	12.459	545.056	0.589	944.828
	1	14.473	0.937						
	2	44.289	3.14						
	3	66.33	0.997						
	4	88.39	8.70751017						
	5	93.018	3.051195384						
	6	95.54	5.01478123						
	7	99.09	2.583274312						

Drug release data, Drug content data and particle size measurement data of different microparticles of different formulation.

Formula code	Drug release data			Drug content data					
	Time	Average drug released	Standard deviation	Average drug content (%)	Standard deviation	Average $D_{0.1}$(μm)	Average $D_{0.5}$(μm)	Standard deviation	Average $D_{0.9}$(μm)
Eud(NM,RS)-V1	0.5	73.04	0.316	76.46%	0.51	11.444	50.193	0.884	156.620
	1	86.85	1.123						
	1.5	88.42	5.6163						
	2.25	99.75	3.792						
Theo – A1	0.5	7.036	0.6166	70.88%	0.632	61.353	189.710	0.887	189.710
	1	14.473	0.937						
	2	44.289	3.14						
	3	66.33	0.997						
	4	88.39	8.70751017						
	5	93.018	3.051195384						
	6	95.54	5.01478123						
	7	99.09	2.583274312						

Drug release data, Drug content data and particle size measurement data of different microparticles of different formulation.

Formula code	Drug release data			Drug content data					
	Time	Average drug released	Standard deviation	Average drug content (%)	Standard deviation	Average $D_{0.1(\mu m)}$	Average $D_{0.5}(\mu m)$	Standard deviation	Average $D_{0.9}(\mu m)$
Eud(NM,RS) –B2	0.5	12.56	0.88	95.67	0.62	5.295	21.733	0.918	67.362
	1	47.333	4.21						
	2	70.01	8.28						
	3	88.03	1.300						
	4	88.038	16.266						
	5	92.27	5.817						
	6	92.27	7.77						
	7	98.27	7.779						
Eud (NM,Rs) –B3	0.5	11.39	0.6166	99.23%	3.68	6.792	41.797	3.68	550.467
	1	12.565	0.937						
	2	32.538	3.14						
	3	70.015	0.997						
	4	88.034	8.70751017						
	5	92.27	3.051195384						
	6	95.54	5.01478123						
	7	99.09	2.583274312						

Drug release data, Drug content data and particle size measurement data of different microparticles of different formulation.

Formula code	Drug release data			Drug content data					
	Time	Average drug released	Standard deviation	Average drug content (%)	Standard deviation	Average $D_{0.1(\mu m)}$	Average $D_{0.5}(\mu m)$	Standard deviation	Average $D_{0.9}(\mu m)$
Theo – A2	0.5	39.73	0.029	79.8%	0.593	27.965	499.287	0.593	908.406
	1	80.81	1.41						
	2	91.62	1.76						
	3	93.31	2.23						
	4	95.83	1.916						
	5	99.193	4.87						
Theo – A3	0.5	11.39	0.6166	80.9%	3.68	9.457	43.727	0.95	145.556
	1	12.565	0.937						
	2	32.538	3.14						
	3	70.015	0.997						
	4	88.034	8.70751017						
	5	92.27	3.051195384						
	6	95.54	5.01478123						
	7	99.09	2.583274312						

Drug release data, Drug content data and particle size measurement data of different microparticles of different formulation.

Formula code	Drug release data			Drug content data					
	Time	Average drug released	Standard deviation	Average drug content (%)	Standard deviation	Average $D_{0.1(\mu m)}$	Average $D_{0.5}(\mu m)$	Standard deviation	Average $D_{0.9}(\mu m)$
Eud(NM,RS) –T2	0.5	12.56	0.88	95.67	0.502	27.732	556.556	0.486	894.436
	1	47.333	4.21						
	2	70.01	8.28						
	3	88.03	1.300						
	4	88.038	16.266						
	5	92.27	5.817						
	6	92.27	7.77						
	7	98.27	7.779						
SLS – A1	0.5	13.15	0.6166	80.1%	3.33	14.812	89.094	3.33	855.136
	1	53.72	0.937						
	2	32.538	3.14						
	3	87.73	0.997						
	4	93.27	8.707						
	5	98.95	2.23						
	6	98.952	2.23						
	7	98.952	2.232						

Drug release data, Drug content data and particle size measurement data of different microparticles of different formulation.

Formula code	Drug release data			Drug content data					
	Time	Average drug released	Standard deviation	Average drug content (%)	Standard deviation	Average $D_{0.1(\mu m)}$	Average $D_{0.5}(\mu m)$	Standard deviation	Average $D_{0.9}(\mu m)$
SLS – A2	0.5	26.955	0.033	80.4%	0.412	11.949	98.543	0.886	293.45
	1	47.333	0.395						
	2	31.495	8.28						
	3	66.620	1.300						
	4	74.002	0.236						
	5	83.36	3.38						
	6	90.64	2.75						
	7	99.625	2.75						
SLS – A3	0.5	13.15	0.540	80.69%	0.354	474.508	683.149	0.213	938.829
	1	53.719	0.644						
	2	77.23	1.207						
	3	92.33	2.711						
	4	93.277	1.712						
	5	98.952	2.2398						
	6	98.952	2.238						
	7	98.95	2.2328						

Drug release data, Drug content data and particle size measurement data of different microparticles of different formulation.

Formula code	Drug release data			Drug content data					
	Time	Average drug released	Standard deviation	Average drug content (%)	Standard deviation	Average $D_{0.1(\mu m)}$	Average $D_{0.5}(\mu m)$	Standard deviation	Average $D_{0.9}(\mu m)$
SLS – A4	0.5	12.199	0.545	80.4%	0.412	11.949	98.543	0.886	293.45
	1	94.238	1.6172						
	2	98.27	1.1912						
	3	98.478	8.609						
	4	98.823	6.444						
	5	98.823	6.4						
	6	98.823	6.4144						
	7	98.823	6.4151314						
TW 20 – A1	0.5	47.983	0.9972	80.1%	0.513	16.536	74.855	2.04	542.754
	1	54.046	5.873						
	2	62.456	6.7821						
	3	88.291	2.5265						

Drug release data, Drug content data and particle size measurement data of different microparticles of different formulation.

Formula code	Drug release data			Drug content data					
	Time	Average drug released	Standard deviation	Average drug content (%)	Standard deviation	Average $D_{0.1}$(µm)	Average $D_{0.5}$(µm)	Standard deviation	Average $D_{0.9}$(µm)
TW20- A2	0.5	26.292	1.469	80.1%	0.643	9.092	75.012	3.09	619.316
	1	88.017	1.460						
	2	87.667	0.597						
	3	93.429	4.118						
	4	99.088	4.1215						
	5	99.088	1.469						
	6	99.088	6.491						
LT- F68 – A1	0.5	6.494	0.0547	92.2%	0.123	10.569	53.552	0.831	151.953
	1	68.220	0.0547						
	2	92.673	1.725						
	3	97.478	1.425						
	4	98.977	0.0549						

Drug release data, Drug content data and particle size measurement data of different microparticles of different formulation.

Formula code	Drug release data			Drug content data					
	Time	Average drug released	Standard deviation	Average drug content (%)	Standard deviation	Average $D_{0.1(\mu m)}$	Average $D_{0.5}(\mu m)$	Standard deviation	Average $D_{0.9}(\mu m)$
LT – F68- A2	0.5	20.768	0.644	96.96%	0.943	11.795%	44.643	0.883	144.972
	1	90.862	0.674						
	2	98.757	1.5444717						

تحضير الحبيبات للمواد الفعَاله الذائبه في الماء والمحضره باستخدام طريقة تبخير المذيب و دراسة أثر تغير بعض عوامل التحضير على شكل الحبيبات و اطلاق الماده الفعاله منها.

اعداد
ألاء أحمد عمر الطاهر

المشرف
الدكتور بشَار الخالدي

الملخص

تحضير الحبيبات المحملة بطريقة تبخير المذيب باستخدام ايودرجت(ن م) و (ر ل) المحملة بالثيوفلين الذائب في الماء والمحضر باستخدام الصوديوم لوريل سلفيت و توين ٢٠ واللترول ف ٦٨ والتي تم تحضريها باستخدام عوامل تحضير مختلفة، والتي تتضمن١- دراسة أثر درجة الحرارة حيث تم رفع درجة الحرارة من ٢٥ س إلى ٤٠ س ، ٢- نسب المادة الموزعة الى الماده الكليه و٣- كمية المادة الفعالة (الثيوفلين) في المادة الموزعة.

تم معاينة هذه الحبيبات من خلال طرق إطلاق الدواء منها و حجم الحبيبات ، فعند زيادة نسبة الايودرجت ن م و الايودرجت ر ل ، فإن كمية الدواء المحتواة فيها تزداد، وكذلك عند زيادة المادة المثبتة فيها، فإن هنالك زيادة قليله في كمية الدواء المحتواة وعند زيادة حجم المادة الموزعة من ٥% إلى١٠%، فإن هنالك نقصان طفيف في حجم الحبيبات، ولكن عند رفع نسبة المادة الموزعة إلى ١٥ %، فإن حجم الحبيبات تزداد.

و عند دراسة أثر الحرارة، ففقد لوحظ أنه عند رفعها من ٢٥ س إلى ٤٠ س، فإن حجم الحبيبات تزداد.